

## 251 Human Secreted Proteins

### *Related Applications*

This application is a continuation-in-part of PCT/US02/08124, filed March 19, 2002, which in turn claims benefit of the following:

10

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
PCT/US02/08124	Continuation-in-part of	10/100,683	03/19/02
10/100,683	Non-provisional of	60/277,340	03/21/01
10/100,683	Non-provisional of	60/306,171	07/19/01
10/100,683	Non-provisional of	60/331,287	11/13/01
10/100,683	Continuation-in-part of	09/981,876	10/19/01
09/981,876	Divisional of	09/621,011	07/20/00
09/621,011	Continuation of	09/148,545	09/04/98
09/148,545	Continuation-in-part of	PCT/US98/04482	03/06/98
10/100,683	Continuation-in-part of	09/621,011	07/20/00
09/621,011	Continuation of	09/148,545	09/04/98
09/148,545	Continuation-in-part of	PCT/US98/04482	03/06/98
10/100,683	Continuation-in-part of	09/148,545	09/04/98
09/148,545	Continuation-in-part of	PCT/US98/04482	03/06/98
10/100,683	Continuation-in-part of	PCT/US98/04482	03/06/98
PCT/US98/04482	Non-provisional of	60/040,162	03/07/97
PCT/US98/04482	Non-provisional of	60/040,333	03/07/97
PCT/US98/04482	Non-provisional of	60/038,621	03/07/97
PCT/US98/04482	Non-provisional of	60/040,161	03/07/97
PCT/US98/04482	Non-provisional of	60/040,626	03/07/97
PCT/US98/04482	Non-provisional of	60/040,334	03/07/97
PCT/US98/04482	Non-provisional of	60/040,336	03/07/97
PCT/US98/04482	Non-provisional of	60/040,163	03/07/97
PCT/US98/04482	Non-provisional of	60/047,615	05/23/97
PCT/US98/04482	Non-provisional of	60/047,600	05/23/97
PCT/US98/04482	Non-provisional of	60/047,597	05/23/97
PCT/US98/04482	Non-provisional of	60/047,502	05/23/97
PCT/US98/04482	Non-provisional of	60/047,633	05/23/97
PCT/US98/04482	Non-provisional of	60/047,583	05/23/97
PCT/US98/04482	Non-provisional of	60/047,617	05/23/97
PCT/US98/04482	Non-provisional of	60/047,618	05/23/97
PCT/US98/04482	Non-provisional of	60/047,503	05/23/97
PCT/US98/04482	Non-provisional of	60/047,592	05/23/97
PCT/US98/04482	Non-provisional of	60/047,581	05/23/97
PCT/US98/04482	Non-provisional of	60/047,584	05/23/97
PCT/US98/04482	Non-provisional of	60/047,500	05/23/97
PCT/US98/04482	Non-provisional of	60/047,587	05/23/97
PCT/US98/04482	Non-provisional of	60/047,492	05/23/97
PCT/US98/04482	Non-provisional of	60/047,598	05/23/97

PCT/US98/04482	Non-provisional of	60/047,613	05/23/97
PCT/US98/04482	Non-provisional of	60/047,582	05/23/97
PCT/US98/04482	Non-provisional of	60/047,596	05/23/97
PCT/US98/04482	Non-provisional of	60/047,612	05/23/97
PCT/US98/04482	Non-provisional of	60/047,632	05/23/97
PCT/US98/04482	Non-provisional of	60/047,601	05/23/97
PCT/US98/04482	Non-provisional of	60/043,580	04/11/97
PCT/US98/04482	Non-provisional of	60/043,568	04/11/97
PCT/US98/04482	Non-provisional of	60/043,314	04/11/97
PCT/US98/04482	Non-provisional of	60/043,569	04/11/97
PCT/US98/04482	Non-provisional of	60/043,311	04/11/97
PCT/US98/04482	Non-provisional of	60/043,671	04/11/97
PCT/US98/04482	Non-provisional of	60/043,674	04/11/97
PCT/US98/04482	Non-provisional of	60/043,669	04/11/97
PCT/US98/04482	Non-provisional of	60/043,312	04/11/97
PCT/US98/04482	Non-provisional of	60/043,313	04/11/97
PCT/US98/04482	Non-provisional of	60/043,672	04/11/97
PCT/US98/04482	Non-provisional of	60/043,315	04/11/97
PCT/US98/04482	Non-provisional of	60/048,974	06/06/97
PCT/US98/04482	Non-provisional of	60/056,886	08/22/97
PCT/US98/04482	Non-provisional of	60/056,877	08/22/97
PCT/US98/04482	Non-provisional of	60/056,889	08/22/97
PCT/US98/04482	Non-provisional of	60/056,893	08/22/97
PCT/US98/04482	Non-provisional of	60/056,630	08/22/97
PCT/US98/04482	Non-provisional of	60/056,878	08/22/97
PCT/US98/04482	Non-provisional of	60/056,662	08/22/97
PCT/US98/04482	Non-provisional of	60/056,872	08/22/97
PCT/US98/04482	Non-provisional of	60/056,882	08/22/97
PCT/US98/04482	Non-provisional of	60/056,637	08/22/97
PCT/US98/04482	Non-provisional of	60/056,903	08/22/97
PCT/US98/04482	Non-provisional of	60/056,888	08/22/97
PCT/US98/04482	Non-provisional of	60/056,879	08/22/97
PCT/US98/04482	Non-provisional of	60/056,880	08/22/97
PCT/US98/04482	Non-provisional of	60/056,894	08/22/97
PCT/US98/04482	Non-provisional of	60/056,911	08/22/97
PCT/US98/04482	Non-provisional of	60/056,636	08/22/97
PCT/US98/04482	Non-provisional of	60/056,874	08/22/97
PCT/US98/04482	Non-provisional of	60/056,910	08/22/97
PCT/US98/04482	Non-provisional of	60/056,864	08/22/97
PCT/US98/04482	Non-provisional of	60/056,631	08/22/97
PCT/US98/04482	Non-provisional of	60/056,845	08/22/97
PCT/US98/04482	Non-provisional of	60/056,892	08/22/97
PCT/US98/04482	Non-provisional of	60/047,595	05/23/97
PCT/US98/04482	Non-provisional of	60/057,761	09/05/97
PCT/US98/04482	Non-provisional of	60/047,599	05/23/97
PCT/US98/04482	Non-provisional of	60/047,588	05/23/97
PCT/US98/04482	Non-provisional of	60/047,585	05/23/97
PCT/US98/04482	Non-provisional of	60/047,586	05/23/97
PCT/US98/04482	Non-provisional of	60/047,590	05/23/97
PCT/US98/04482	Non-provisional of	60/047,594	05/23/97
PCT/US98/04482	Non-provisional of	60/047,589	05/23/97
PCT/US98/04482	Non-provisional of	60/047,593	05/23/97
PCT/US98/04482	Non-provisional of	60/047,614	05/23/97



PCT/US98/04482	Non-provisional of	60/043,578	04/11/97
PCT/US98/04482	Non-provisional of	60/043,576	04/11/97
PCT/US98/04482	Non-provisional of	60/047,501	05/23/97
PCT/US98/04482	Non-provisional of	60/043,670	04/11/97
PCT/US98/04482	Non-provisional of	60/056,632	08/22/97
PCT/US98/04482	Non-provisional of	60/056,664	08/22/97
PCT/US98/04482	Non-provisional of	60/056,876	08/22/97
PCT/US98/04482	Non-provisional of	60/056,881	08/22/97
PCT/US98/04482	Non-provisional of	60/056,909	08/22/97
PCT/US98/04482	Non-provisional of	60/056,875	08/22/97
PCT/US98/04482	Non-provisional of	60/056,862	08/22/97
PCT/US98/04482	Non-provisional of	60/056,887	08/22/97
PCT/US98/04482	Non-provisional of	60/056,908	08/22/97
PCT/US98/04482	Non-provisional of	60/048,964	06/06/97
PCT/US98/04482	Non-provisional of	60/057,650	09/05/97
PCT/US98/04482	Non-provisional of	60/056,884	08/22/97
10/100,683	Continuation-in-part of	09/882,171	06/18/01
09/882,171	Non-provisional of	60/190,068	03/17/00
09/882,171	Continuation of	09/809,391	03/16/01
09/809,391	Continuation-in-part of	09/149,476	09/08/98
09/149,476	Continuation-in-part of	PCT/US98/04493	03/06/98
10/100,683	Continuation-in-part of	09/809,391	03/16/01
09/809,391	Non-provisional of	60/190,068	03/17/00
09/809,391	Continuation-in-part of	09/149,476	09/08/98
09/149,476	Continuation-in-part of	PCT/US98/04493	03/06/98
10/100,683	Continuation-in-part of	09/149,476	09/08/98
09/149,476	Continuation-in-part of	PCT/US98/04493	03/06/98
10/100,683	Continuation-in-part of	PCT/US98/04493	03/06/98
PCT/US98/04493	Non-provisional of	60/040,161	03/07/97
PCT/US98/04493	Non-provisional of	60/040,162	03/07/97
PCT/US98/04493	Non-provisional of	60/040,333	03/07/97
PCT/US98/04493	Non-provisional of	60/038,621	03/07/97
PCT/US98/04493	Non-provisional of	60/040,626	03/07/97
PCT/US98/04493	Non-provisional of	60/040,334	03/07/97
PCT/US98/04493	Non-provisional of	60/040,336	03/07/97
PCT/US98/04493	Non-provisional of	60/040,163	03/07/97
PCT/US98/04493	Non-provisional of	60/047,600	05/23/97
PCT/US98/04493	Non-provisional of	60/047,615	05/23/97
PCT/US98/04493	Non-provisional of	60/047,597	05/23/97
PCT/US98/04493	Non-provisional of	60/047,502	05/23/97
PCT/US98/04493	Non-provisional of	60/047,633	05/23/97
PCT/US98/04493	Non-provisional of	60/047,583	05/23/97
PCT/US98/04493	Non-provisional of	60/047,617	05/23/97
PCT/US98/04493	Non-provisional of	60/047,618	05/23/97
PCT/US98/04493	Non-provisional of	60/047,503	05/23/97
PCT/US98/04493	Non-provisional of	60/047,592	05/23/97
PCT/US98/04493	Non-provisional of	60/047,581	05/23/97
PCT/US98/04493	Non-provisional of	60/047,584	05/23/97
PCT/US98/04493	Non-provisional of	60/047,500	05/23/97
PCT/US98/04493	Non-provisional of	60/047,587	05/23/97
PCT/US98/04493	Non-provisional of	60/047,492	05/23/97
PCT/US98/04493	Non-provisional of	60/047,598	05/23/97
PCT/US98/04493	Non-provisional of	60/047,613	05/23/97

PCT/US98/04493	Non-provisional of	60/047,582	05/23/97
PCT/US98/04493	Non-provisional of	60/047,596	05/23/97
PCT/US98/04493	Non-provisional of	60/047,612	05/23/97
PCT/US98/04493	Non-provisional of	60/047,632	05/23/97
PCT/US98/04493	Non-provisional of	60/047,601	05/23/97
PCT/US98/04493	Non-provisional of	60/043,580	04/11/97
PCT/US98/04493	Non-provisional of	60/043,568	04/11/97
PCT/US98/04493	Non-provisional of	60/043,314	04/11/97
PCT/US98/04493	Non-provisional of	60/043,569	04/11/97
PCT/US98/04493	Non-provisional of	60/043,311	04/11/97
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PCT/US98/04493	Non-provisional of	60/043,674	04/11/97
PCT/US98/04493	Non-provisional of	60/043,669	04/11/97
PCT/US98/04493	Non-provisional of	60/043,312	04/11/97
PCT/US98/04493	Non-provisional of	60/043,313	04/11/97
PCT/US98/04493	Non-provisional of	60/043,672	04/11/97
PCT/US98/04493	Non-provisional of	60/043,315	04/11/97
PCT/US98/04493	Non-provisional of	60/048,974	06/06/97
PCT/US98/04493	Non-provisional of	60/056,886	08/22/97
PCT/US98/04493	Non-provisional of	60/056,877	08/22/97
PCT/US98/04493	Non-provisional of	60/056,889	08/22/97
PCT/US98/04493	Non-provisional of	60/056,893	08/22/97
PCT/US98/04493	Non-provisional of	60/056,630	08/22/97
PCT/US98/04493	Non-provisional of	60/056,878	08/22/97
PCT/US98/04493	Non-provisional of	60/056,662	08/22/97
PCT/US98/04493	Non-provisional of	60/056,872	08/22/97
PCT/US98/04493	Non-provisional of	60/056,882	08/22/97
PCT/US98/04493	Non-provisional of	60/056,637	08/22/97
PCT/US98/04493	Non-provisional of	60/056,903	08/22/97
PCT/US98/04493	Non-provisional of	60/056,888	08/22/97
PCT/US98/04493	Non-provisional of	60/056,879	08/22/97
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PCT/US98/04493	Non-provisional of	60/056,894	08/22/97
PCT/US98/04493	Non-provisional of	60/056,911	08/22/97
PCT/US98/04493	Non-provisional of	60/056,636	08/22/97
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PCT/US98/04493	Non-provisional of	60/056,864	08/22/97
PCT/US98/04493	Non-provisional of	60/056,631	08/22/97
PCT/US98/04493	Non-provisional of	60/056,845	08/22/97
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PCT/US98/04493	Non-provisional of	60/047,593	05/23/97
PCT/US98/04493	Non-provisional of	60/047,614	05/23/97
PCT/US98/04493	Non-provisional of	60/043,578	04/11/97

PCT/US98/04493	Non-provisional of	60/043,576	04/11/97
PCT/US98/04493	Non-provisional of	60/047,501	05/23/97
PCT/US98/04493	Non-provisional of	60/043,670	04/11/97
PCT/US98/04493	Non-provisional of	60/056,632	08/22/97
PCT/US98/04493	Non-provisional of	60/056,664	08/22/97
PCT/US98/04493	Non-provisional of	60/056,876	08/22/97
PCT/US98/04493	Non-provisional of	60/056,881	08/22/97
PCT/US98/04493	Non-provisional of	60/056,909	08/22/97
PCT/US98/04493	Non-provisional of	60/056,875	08/22/97
PCT/US98/04493	Non-provisional of	60/056,862	08/22/97
PCT/US98/04493	Non-provisional of	60/056,887	08/22/97
PCT/US98/04493	Non-provisional of	60/056,908	08/22/97
PCT/US98/04493	Non-provisional of	60/048,964	06/06/97
PCT/US98/04493	Non-provisional of	60/057,650	09/05/97
PCT/US98/04493	Non-provisional of	60/056,884	08/22/97
PCT/US98/04493	Non-provisional of	60/057,669	09/05/97
PCT/US98/04493	Non-provisional of	60/049,610	06/13/97
PCT/US98/04493	Non-provisional of	60/061,060	10/02/97
PCT/US98/04493	Non-provisional of	60/051,926	07/08/97
PCT/US98/04493	Non-provisional of	60/052,874	07/16/97
PCT/US98/04493	Non-provisional of	60/058,785	09/12/97
PCT/US98/04493	Non-provisional of	60/055,724	08/18/97
10/100,683	Continuation-in-part of	10/058,993	01/30/02
10/058,993	Non-provisional of	60/265,583	02/02/01
10/058,993	Continuation-in-part of	09/852,659	05/11/01
09/852,659	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/058,993	Continuation-in-part of	09/853,161	05/11/01
09/853,161	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/058,993	Continuation-in-part of	09/852,797	05/11/01
09/852,797	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/100,683	Continuation-in-part of	09/852,659	05/11/01
09/852,659	Non-provisional of	60/265,583	02/02/01
09/852,659	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/100,683	Continuation-in-part of	09/853,161	05/11/01
09/853,161	Non-provisional of	60/265,583	02/02/01
09/853,161	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/100,683	Continuation-in-part of	09/852,797	05/11/01
09/852,797	Non-provisional of	60/265,583	02/02/01
09/852,797	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/100,683	Continuation-in-part of	09/152,060	09/11/98
09/152,060	Continuation-in-part of	PCT/US98/04858	03/12/98
10/100,683	Continuation-in-part of	PCT/US98/04858	03/12/98
PCT/US98/04858	Non-provisional of	60/040,762	03/14/97
PCT/US98/04858	Non-provisional of	60/040,710	03/14/97
PCT/US98/04858	Non-provisional of	60/050,934	05/30/97
PCT/US98/04858	Non-provisional of	60/048,100	05/30/97
PCT/US98/04858	Non-provisional of	60/048,357	05/30/97

PCT/US98/04858	Non-provisional of	60/048,189	05/30/97
PCT/US98/04858	Non-provisional of	60/057,765	09/05/97
PCT/US98/04858	Non-provisional of	60/048,970	06/06/97
PCT/US98/04858	Non-provisional of	60/068,368	12/19/97
10/100,683	Continuation-in-part of	10/059,395	01/31/02
10/059,395	Divisional of	09/966,262	10/01/01
09/966,262	Continuation of	09/154,707	09/17/98
09/154,707	Continuation-in-part of	PCT/US98/05311	03/19/98
10/100,683	Continuation-in-part of	09/984,245	10/29/01
09/984,245	Divisional of	09/154,707	09/17/98
09/154,707	Continuation-in-part of	PCT/US98/05311	03/19/98
10/100,683	Continuation-in-part of	09/983,966	10/26/01
09/983,966	Divisional of	09/154,707	09/17/98
09/154,707	Continuation-in-part of	PCT/US98/05311	03/19/98
10/100,683	Continuation-in-part of	09/966,262	10/01/01
09/966,262	Continuation of of	09/154,707	09/17/98
09/154,707	Continuation-in-part of	PCT/US98/05311	03/19/98
10/100,683	Continuation-in-part of	09/154,707	09/17/98
09/154,707	Continuation-in-part of	PCT/US98/05311	03/19/98
10/100,683	Continuation-in-part of	PCT/US98/05311	03/03/98
PCT/US98/05311	Non-provisional of	60/041,277	03/21/97
PCT/US98/05311	Non-provisional of	60/042,344	03/21/97
PCT/US98/05311	Non-provisional of	60/041,276	03/21/97
PCT/US98/05311	Non-provisional of	60/041,281	03/21/97
PCT/US98/05311	Non-provisional of	60/048,094	05/30/97
PCT/US98/05311	Non-provisional of	60/048,350	05/30/97
PCT/US98/05311	Non-provisional of	60/048,188	05/30/97
PCT/US98/05311	Non-provisional of	60/048,135	05/30/97
PCT/US98/05311	Non-provisional of	60/050,937	05/30/97
PCT/US98/05311	Non-provisional of	60/048,187	05/30/97
PCT/US98/05311	Non-provisional of	60/048,099	05/30/97
PCT/US98/05311	Non-provisional of	60/048,352	05/30/97
PCT/US98/05311	Non-provisional of	60/048,186	05/30/97
PCT/US98/05311	Non-provisional of	60/048,069	05/30/97
PCT/US98/05311	Non-provisional of	60/048,095	05/30/97
PCT/US98/05311	Non-provisional of	60/048,131	05/30/97
PCT/US98/05311	Non-provisional of	60/048,096	05/30/97
PCT/US98/05311	Non-provisional of	60/048,355	05/30/97
PCT/US98/05311	Non-provisional of	60/048,160	05/30/97
PCT/US98/05311	Non-provisional of	60/048,351	05/30/97
PCT/US98/05311	Non-provisional of	60/048,154	05/30/97
PCT/US98/05311	Non-provisional of	60/054,804	08/05/97
PCT/US98/05311	Non-provisional of	60/056,370	08/19/97
PCT/US98/05311	Non-provisional of	60/060,862	10/02/97
10/100,683	Continuation-in-part of	09/814,122	03/22/01
09/814,122	Continuation of	09/577,145	05/24/00
09/577,145	Continuation of	09/166,780	10/06/98
09/166,780	Continuation-in-part of	PCT/US98/06801	04/07/98
10/100,683	Continuation-in-part of	PCT/US98/06801	04/07/98
PCT/US98/06801	Non-provisional of	60/042,726	04/08/97
PCT/US98/06801	Non-provisional of	60/042,727	04/08/97
PCT/US98/06801	Non-provisional of	60/042,728	04/08/97

PCT/US98/06801	Non-provisional of	60/042,754	04/08/97
PCT/US98/06801	Non-provisional of	60/042,825	04/08/97
PCT/US98/06801	Non-provisional of	60/048,068	05/30/97
PCT/US98/06801	Non-provisional of	60/048,070	05/30/97
PCT/US98/06801	Non-provisional of	60/048,184	05/30/97
10/100,683	Continuation-in-part of	PCT/US98/06801	04/07/97
PCT/US98/06801	Non-provisional of	60/042,726	04/08/97
PCT/US98/06801	Non-provisional of	60/042,727	04/08/97
PCT/US98/06801	Non-provisional of	60/042,728	04/08/97
PCT/US98/06801	Non-provisional of	60/042,754	04/08/97
PCT/US98/06801	Non-provisional of	60/042,825	04/08/97
PCT/US98/06801	Non-provisional of	60/048,068	05/30/97
PCT/US98/06801	Non-provisional of	60/048,070	05/30/97
PCT/US98/06801	Non-provisional of	60/048,184	05/30/97
10/100,683	Continuation-in-part of	PCT/US98/10868	05/28/98
PCT/US98/10868	Non-provisional of	60/044,039	05/30/97
PCT/US98/10868	Non-provisional of	60/048,093	05/30/97
PCT/US98/10868	Non-provisional of	60/048,190	05/30/97
PCT/US98/10868	Non-provisional of	60/050,935	05/30/97
PCT/US98/10868	Non-provisional of	60/048,101	05/30/97
PCT/US98/10868	Non-provisional of	60/048,356	05/30/97
PCT/US98/10868	Non-provisional of	60/056,250	08/29/97
PCT/US98/10868	Non-provisional of	60/056,296	08/29/97
PCT/US98/10868	Non-provisional of	60/056,293	08/29/97
10/100,683	Continuation-in-part of	PCT/US98/11422	06/04/98
PCT/US98/11422	Non-provisional of	60/048,885	06/06/97
PCT/US98/11422	Non-provisional of	60/049,375	06/06/97
PCT/US98/11422	Non-provisional of	60/048,881	06/06/97
PCT/US98/11422	Non-provisional of	60/048,880	06/06/97
PCT/US98/11422	Non-provisional of	60/048,896	06/06/97
PCT/US98/11422	Non-provisional of	60/049,020	06/06/97
PCT/US98/11422	Non-provisional of	60/048,876	06/06/97
PCT/US98/11422	Non-provisional of	60/048,895	06/06/97
PCT/US98/11422	Non-provisional of	60/048,884	06/06/97
PCT/US98/11422	Non-provisional of	60/048,894	06/06/97
PCT/US98/11422	Non-provisional of	60/048,971	06/06/97
PCT/US98/11422	Non-provisional of	60/048,964	06/06/97
PCT/US98/11422	Non-provisional of	60/048,882	06/06/97
PCT/US98/11422	Non-provisional of	60/048,899	06/06/97
PCT/US98/11422	Non-provisional of	60/048,893	06/06/97
PCT/US98/11422	Non-provisional of	60/048,900	06/06/97
PCT/US98/11422	Non-provisional of	60/048,901	06/06/97
PCT/US98/11422	Non-provisional of	60/048,892	06/06/97
PCT/US98/11422	Non-provisional of	60/048,915	06/06/97
PCT/US98/11422	Non-provisional of	60/049,019	06/06/97
PCT/US98/11422	Non-provisional of	60/048,970	06/06/97
PCT/US98/11422	Non-provisional of	60/048,972	06/06/97
PCT/US98/11422	Non-provisional of	60/048,916	06/06/97
PCT/US98/11422	Non-provisional of	60/049,373	06/06/97
PCT/US98/11422	Non-provisional of	60/048,875	06/06/97
PCT/US98/11422	Non-provisional of	60/049,374	06/06/97
PCT/US98/11422	Non-provisional of	60/048,917	06/06/97
PCT/US98/11422	Non-provisional of	60/048,949	06/06/97

PCT/US98/11422	Non-provisional of	60/048,974	06/06/97
PCT/US98/11422	Non-provisional of	60/048,883	06/06/97
PCT/US98/11422	Non-provisional of	60/048,897	06/06/97
PCT/US98/11422	Non-provisional of	60/048,898	06/06/97
PCT/US98/11422	Non-provisional of	60/048,962	06/06/97
PCT/US98/11422	Non-provisional of	60/048,963	06/06/97
PCT/US98/11422	Non-provisional of	60/048,877	06/06/97
PCT/US98/11422	Non-provisional of	60/048,878	06/06/97
PCT/US98/11422	Non-provisional of	60/057,645	09/05/97
PCT/US98/11422	Non-provisional of	60/057,642	09/05/97
PCT/US98/11422	Non-provisional of	60/057,668	09/05/97
PCT/US98/11422	Non-provisional of	60/057,635	09/05/97
PCT/US98/11422	Non-provisional of	60/057,627	09/05/97
PCT/US98/11422	Non-provisional of	60/057,667	09/05/97
PCT/US98/11422	Non-provisional of	60/057,666	09/05/97
PCT/US98/11422	Non-provisional of	60/057,764	09/05/97
PCT/US98/11422	Non-provisional of	60/057,643	09/05/97
PCT/US98/11422	Non-provisional of	60/057,769	09/05/97
PCT/US98/11422	Non-provisional of	60/057,763	09/05/97
PCT/US98/11422	Non-provisional of	60/057,650	09/05/97
PCT/US98/11422	Non-provisional of	60/057,584	09/05/97
PCT/US98/11422	Non-provisional of	60/057,647	09/05/97
PCT/US98/11422	Non-provisional of	60/057,661	09/05/97
PCT/US98/11422	Non-provisional of	60/057,662	09/05/97
PCT/US98/11422	Non-provisional of	60/057,646	09/05/97
PCT/US98/11422	Non-provisional of	60/057,654	09/05/97
PCT/US98/11422	Non-provisional of	60/057,651	09/05/97
PCT/US98/11422	Non-provisional of	60/057,644	09/05/97
PCT/US98/11422	Non-provisional of	60/057,765	09/05/97
PCT/US98/11422	Non-provisional of	60/057,762	09/05/97
PCT/US98/11422	Non-provisional of	60/057,775	09/05/97
PCT/US98/11422	Non-provisional of	60/057,648	09/05/97
PCT/US98/11422	Non-provisional of	60/057,774	09/05/97
PCT/US98/11422	Non-provisional of	60/057,649	09/05/97
PCT/US98/11422	Non-provisional of	60/057,770	09/05/97
PCT/US98/11422	Non-provisional of	60/057,771	09/05/97
PCT/US98/11422	Non-provisional of	60/057,761	09/05/97
PCT/US98/11422	Non-provisional of	60/057,760	09/05/97
PCT/US98/11422	Non-provisional of	60/057,776	09/05/97
PCT/US98/11422	Non-provisional of	60/057,778	09/05/97
PCT/US98/11422	Non-provisional of	60/057,629	09/05/97
PCT/US98/11422	Non-provisional of	60/057,628	09/05/97
PCT/US98/11422	Non-provisional of	60/057,777	09/05/97
PCT/US98/11422	Non-provisional of	60/057,634	09/05/97
PCT/US98/11422	Non-provisional of	60/070,923	12/18/97
10/100,683	Continuation-in-part of	PCT/US01/05614	02/21/01
PCT/US01/05614	Non-provisional of	60/184,836	02/24/00
PCT/US01/05614	Non-provisional of	60/193,170	03/29/00
10/100,683	Continuation-in-part of	PCT/US98/12125	06/11/98
PCT/US98/12125	Non-provisional of	60/049,547	06/13/97
PCT/US98/12125	Non-provisional of	60/049,548	06/13/97
PCT/US98/12125	Non-provisional of	60/049,549	06/13/97
PCT/US98/12125	Non-provisional of	60/049,550	06/13/97

PCT/US98/12125	Non-provisional of	60/049,566	06/13/97
PCT/US98/12125	Non-provisional of	60/049,606	06/13/97
PCT/US98/12125	Non-provisional of	60/049,607	06/13/97
PCT/US98/12125	Non-provisional of	60/049,608	06/13/97
PCT/US98/12125	Non-provisional of	60/049,609	06/13/97
PCT/US98/12125	Non-provisional of	60/049,610	06/13/97
PCT/US98/12125	Non-provisional of	60/049,611	06/13/97
PCT/US98/12125	Non-provisional of	60/050,901	06/13/97
PCT/US98/12125	Non-provisional of	60/052,989	06/13/97
PCT/US98/12125	Non-provisional of	60/051,919	07/08/97
PCT/US98/12125	Non-provisional of	60/055,984	08/18/97
PCT/US98/12125	Non-provisional of	60/058,665	09/12/97
PCT/US98/12125	Non-provisional of	60/058,668	09/12/97
PCT/US98/12125	Non-provisional of	60/058,669	09/12/97
PCT/US98/12125	Non-provisional of	60/058,750	09/12/97
PCT/US98/12125	Non-provisional of	60/058,971	09/12/97
PCT/US98/12125	Non-provisional of	60/058,972	09/12/97
PCT/US98/12125	Non-provisional of	60/058,975	09/12/97
PCT/US98/12125	Non-provisional of	60/060,834	10/02/97
PCT/US98/12125	Non-provisional of	60/060,841	10/02/97
PCT/US98/12125	Non-provisional of	60/060,844	10/02/97
PCT/US98/12125	Non-provisional of	60/060,865	10/02/97
PCT/US98/12125	Non-provisional of	60/061,059	10/02/97
PCT/US98/12125	Non-provisional of	60/061,060	10/02/97
10/100,683	Continuation-in-part of	09/627,081	07/27/00
09/627,081	Continuation of	09/213,365	12/17/98
09/213,365	Continuation-in-part of	PCT/US98/13608	06/30/98
10/100,683	Continuation-in-part of	PCT/US98/13608	06/30/98
PCT/US98/13608	Non-provisional of	60/051,480	07/01/97
PCT/US98/13608	Non-provisional of	60/051,381	07/01/97
PCT/US98/13608	Non-provisional of	60/058,663	09/12/97
PCT/US98/13608	Non-provisional of	60/058,598	09/12/97
10/100,683	Continuation-in-part of	09/984,490	10/30/01
09/984,490	Divisional of	09/227,357	01/08/99
09/227,357	Continuation-in-part of	PCT/US98/13684	07/07/98
10/100,683	Continuation-in-part of	09/983,802	10/25/01
09/983,802	Continuation of	09/227,357	10/10/01
09/227,357	Continuation-in-part of	PCT/US98/13684	07/07/98
10/100,683	Continuation-in-part of	09/973,278	10/10/01
09/973,278	Non-provisional of	60/239,899	10/13/00
09/973,278	Continuation-in-part of	09/227,357	01/08/99
09/227,357	Continuation-in-part of	PCT/US98/13684	07/07/98
10/100,683	Continuation-in-part of	PCT/US98/13684	07/07/98
PCT/US98/13684	Non-provisional of	60/051,926	07/08/97
PCT/US98/13684	Non-provisional of	60/052,793	07/08/97
PCT/US98/13684	Non-provisional of	60/051,925	07/08/97
PCT/US98/13684	Non-provisional of	60/051,929	07/08/97
PCT/US98/13684	Non-provisional of	60/052,803	07/08/97
PCT/US98/13684	Non-provisional of	60/052,732	07/08/97
PCT/US98/13684	Non-provisional of	60/051,931	07/08/97
PCT/US98/13684	Non-provisional of	60/051,932	07/08/97
PCT/US98/13684	Non-provisional of	60/051,916	07/08/97
PCT/US98/13684	Non-provisional of	60/051,930	07/08/97

PCT/US98/13684	Non-provisional of	60/051,918	07/08/97
PCT/US98/13684	Non-provisional of	60/051,920	07/08/97
PCT/US98/13684	Non-provisional of	60/052,733	07/08/97
PCT/US98/13684	Non-provisional of	60/052,795	07/08/97
PCT/US98/13684	Non-provisional of	60/051,919	07/08/97
PCT/US98/13684	Non-provisional of	60/051,928	07/08/97
PCT/US98/13684	Non-provisional of	60/055,722	08/18/97
PCT/US98/13684	Non-provisional of	60/055,723	08/18/97
PCT/US98/13684	Non-provisional of	60/055,948	08/18/97
PCT/US98/13684	Non-provisional of	60/055,949	08/18/97
PCT/US98/13684	Non-provisional of	60/055,953	08/18/97
PCT/US98/13684	Non-provisional of	60/055,950	08/18/97
PCT/US98/13684	Non-provisional of	60/055,947	08/18/97
PCT/US98/13684	Non-provisional of	60/055,964	08/18/97
PCT/US98/13684	Non-provisional of	60/056,360	08/18/97
PCT/US98/13684	Non-provisional of	60/055,684	08/18/97
PCT/US98/13684	Non-provisional of	60/055,984	08/18/97
PCT/US98/13684	Non-provisional of	60/055,954	08/18/97
PCT/US98/13684	Non-provisional of	60/058,785	09/12/97
PCT/US98/13684	Non-provisional of	60/058,664	09/12/97
PCT/US98/13684	Non-provisional of	60/058,660	09/12/97
PCT/US98/13684	Non-provisional of	60/058,661	09/12/97
10/100,683	Continuation-in-part of	09/776,724	02/06/01
09/776,724	Non-provisional of	60/180,909	02/08/00
09/776,724	Continuation-in-part of	09/669,688	09/26/00
09/669,688	Continuation of	09/229,982	01/14/99
09/229,982	Continuation-in-part of	PCT/US98/14613	07/15/98
10/100,683	Continuation-in-part of	09/669,688	09/26/00
09/669,688	Continuation of	09/229,982	01/14/99
09/229,982	Continuation-in-part of	PCT/US98/14613	07/15/98
10/100,683	Continuation-in-part of	09/229,982	01/14/99
09/229,982	Continuation-in-part of	PCT/US98/14613	07/15/98
10/100,683	Continuation-in-part of	PCT/US98/14613	07/15/98
PCT/US98/14613	Non-provisional of	60/052,661	07/16/97
PCT/US98/14613	Non-provisional of	60/052,872	07/16/97
PCT/US98/14613	Non-provisional of	60/052,871	07/16/97
PCT/US98/14613	Non-provisional of	60/052,874	07/16/97
PCT/US98/14613	Non-provisional of	60/052,873	07/16/97
PCT/US98/14613	Non-provisional of	60/052,870	07/16/97
PCT/US98/14613	Non-provisional of	60/052,875	07/16/97
PCT/US98/14613	Non-provisional of	60/053,440	07/22/97
PCT/US98/14613	Non-provisional of	60/053,441	07/22/97
PCT/US98/14613	Non-provisional of	60/053,442	07/22/97
PCT/US98/14613	Non-provisional of	60/056,359	08/18/97
PCT/US98/14613	Non-provisional of	60/055,725	08/18/97
PCT/US98/14613	Non-provisional of	60/055,985	08/18/97
PCT/US98/14613	Non-provisional of	60/055,952	08/18/97
PCT/US98/14613	Non-provisional of	60/055,989	08/18/97
PCT/US98/14613	Non-provisional of	60/056,361	08/18/97
PCT/US98/14613	Non-provisional of	60/055,726	08/18/97
PCT/US98/14613	Non-provisional of	60/055,724	08/18/97
PCT/US98/14613	Non-provisional of	60/055,946	08/18/97
PCT/US98/14613	Non-provisional of	60/055,683	08/18/97



10/100,683	Non-provisional of	60/295,558	06/05/01
10/100,683	Continuation-in-part of	09/820,649	03/30/01
09/820,649	Continuation of	09/666,984	09/21/00
09/666,984	Continuation of	09/236,557	01/26/99
09/236,557	Continuation-in-part of	PCT/US98/15949	07/29/98
10/100,683	Continuation-in-part of	PCT/US98/15949	07/29/98
PCT/US98/15949	Non-provisional of	60/054,212	07/30/97
PCT/US98/15949	Non-provisional of	60/054,209	07/30/97
PCT/US98/15949	Non-provisional of	60/054,234	07/30/97
PCT/US98/15949	Non-provisional of	60/054,218	07/30/97
PCT/US98/15949	Non-provisional of	60/054,214	07/30/97
PCT/US98/15949	Non-provisional of	60/054,236	07/30/97
PCT/US98/15949	Non-provisional of	60/054,215	07/30/97
PCT/US98/15949	Non-provisional of	60/054,211	07/30/97
PCT/US98/15949	Non-provisional of	60/054,217	07/30/97
PCT/US98/15949	Non-provisional of	60/054,213	07/30/97
PCT/US98/15949	Non-provisional of	60/055,968	08/18/97
PCT/US98/15949	Non-provisional of	60/055,969	08/18/97
PCT/US98/15949	Non-provisional of	60/055,972	08/18/97
PCT/US98/15949	Non-provisional of	60/056,561	08/19/97
PCT/US98/15949	Non-provisional of	60/056,534	08/19/97
PCT/US98/15949	Non-provisional of	60/056,729	08/19/97
PCT/US98/15949	Non-provisional of	60/056,543	08/19/97
PCT/US98/15949	Non-provisional of	60/056,727	08/19/97
PCT/US98/15949	Non-provisional of	60/056,554	08/19/97
PCT/US98/15949	Non-provisional of	60/056,730	08/19/97
10/100,683	Continuation-in-part of	09/969,730	10/04/01
09/969,730	Continuation-in-part of	09/774,639	02/01/01
09/774,639	Continuation of	09/244,112	02/04/99
09/244,112	Continuation-in-part of	PCT/US98/16235	08/04/98
10/100,683	Continuation-in-part of	09/774,639	02/01/01
09/774,639	Continuation of	09/244,112	02/04/99
09/244,112	Continuation-in-part of	PCT/US98/16235	08/04/98
10/100,683	Continuation-in-part of	09/969,730	10/04/01
09/969,730	Non-provisional of	60/238,291	10/06/00
10/100,683	Continuation-in-part of	PCT/US98/16235	08/04/98
PCT/US98/16235	Non-provisional of	60/055,386	08/05/97
PCT/US98/16235	Non-provisional of	60/054,807	08/05/97
PCT/US98/16235	Non-provisional of	60/055,312	08/05/97
PCT/US98/16235	Non-provisional of	60/055,309	08/05/97
PCT/US98/16235	Non-provisional of	60/054,798	08/05/97
PCT/US98/16235	Non-provisional of	60/055,310	08/05/97
PCT/US98/16235	Non-provisional of	60/054,806	08/05/97
PCT/US98/16235	Non-provisional of	60/054,809	08/05/97
PCT/US98/16235	Non-provisional of	60/054,804	08/05/97
PCT/US98/16235	Non-provisional of	60/054,803	08/05/97
PCT/US98/16235	Non-provisional of	60/054,808	08/05/97
PCT/US98/16235	Non-provisional of	60/055,311	08/05/97
PCT/US98/16235	Non-provisional of	60/055,986	08/18/97
PCT/US98/16235	Non-provisional of	60/055,970	08/18/97
PCT/US98/16235	Non-provisional of	60/056,563	08/19/97
PCT/US98/16235	Non-provisional of	60/056,557	08/19/97
PCT/US98/16235	Non-provisional of	60/056,731	08/19/97

PCT/US98/16235	Non-provisional of	60/056,365	08/19/97
PCT/US98/16235	Non-provisional of	60/056,367	08/19/97
PCT/US98/16235	Non-provisional of	60/056,370	08/19/97
PCT/US98/16235	Non-provisional of	60/056,364	08/19/97
PCT/US98/16235	Non-provisional of	60/056,366	08/19/97
PCT/US98/16235	Non-provisional of	60/056,732	08/19/97
PCT/US98/16235	Non-provisional of	60/056,371	08/19/97
10/100,683	Continuation-in-part of	09/716,128	11/17/00
09/716,128	Continuation of	09/251,329	02/17/99
09/251,329	Continuation-in-part of	PCT/US98/17044	08/18/98
10/100,683	Continuation-in-part of	PCT/US98/17044	08/18/98
PCT/US98/17044	Non-provisional of	60/056,555	08/19/97
PCT/US98/17044	Non-provisional of	60/056,556	08/19/97
PCT/US98/17044	Non-provisional of	60/056,535	08/19/97
PCT/US98/17044	Non-provisional of	60/056,629	08/19/97
PCT/US98/17044	Non-provisional of	60/056,369	08/19/97
PCT/US98/17044	Non-provisional of	60/056,628	08/19/97
PCT/US98/17044	Non-provisional of	60/056,728	08/19/97
PCT/US98/17044	Non-provisional of	60/056,368	08/19/97
PCT/US98/17044	Non-provisional of	60/056,726	08/19/97
PCT/US98/17044	Non-provisional of	60/089,510	06/16/98
PCT/US98/17044	Non-provisional of	60/092,956	07/15/98
10/100,683	Continuation-in-part of	09/729,835	12/06/00
09/729,835	Divisional of	09/257,179	02/25/99
09/257,179	Continuation-in-part of	PCT/US98/17709	08/27/98
10/100,683	Continuation-in-part of	09/257,179	02/25/99
09/257,179	Continuation-in-part of	PCT/US98/17709	08/27/98
10/100,683	Continuation-in-part of	PCT/US98/17709	08/27/98
PCT/US98/17709	Non-provisional of	60/056,270	08/29/97
PCT/US98/17709	Non-provisional of	60/056,271	08/29/97
PCT/US98/17709	Non-provisional of	60/056,247	08/29/97
PCT/US98/17709	Non-provisional of	60/056,073	08/29/97
10/100,683	Continuation-in-part of	10/047,021	01/17/02
10/047,021	Continuation-in-part of	09/722,329	11/28/00
09/722,329	Continuation of	09/262,109	03/04/99
09/262,109	Continuation-in-part of	PCT/US98/18360	09/03/98
10/100,683	Continuation-in-part of	09/722,329	11/28/00
09/722,329	Continuation of	09/262,109	03/04/99
09/262,109	Continuation-in-part of	PCT/US98/18360	09/03/98
10/100,683	Continuation-in-part of	PZ016pct2	01/17/02
PZ016pct2	Non-provisional of	60/262,066	01/18/01
10/100,683	Continuation-in-part of	PCT/US98/18360	09/03/98
PCT/US98/18360	Non-provisional of	60/057,626	09/05/97
PCT/US98/18360	Non-provisional of	60/057,663	09/05/97
PCT/US98/18360	Non-provisional of	60/057,669	09/05/97
PCT/US98/18360	Non-provisional of	60/058,667	09/12/97
PCT/US98/18360	Non-provisional of	60/058,974	09/12/97
PCT/US98/18360	Non-provisional of	60/058,973	09/12/97
PCT/US98/18360	Non-provisional of	60/058,666	09/12/97
PCT/US98/18360	Non-provisional of	60/090,112	06/22/98

10/100,683	Continuation-in-part of	09/281,976	03/31/99
09/281,976	Continuation-in-part of	PCT/US98/20775	10/01/98
10/100,683	Continuation-in-part of	PCT/US98/20775	10/01/98
PCT/US98/20775	Non-provisional of	60/060,837	10/02/97
PCT/US98/20775	Non-provisional of	60/060,862	10/02/97
PCT/US98/20775	Non-provisional of	60/060,839	10/02/97
PCT/US98/20775	Non-provisional of	60/060,866	10/02/97
PCT/US98/20775	Non-provisional of	60/060,843	10/02/97
PCT/US98/20775	Non-provisional of	60/060,836	10/02/97
PCT/US98/20775	Non-provisional of	60/060,838	10/02/97
PCT/US98/20775	Non-provisional of	60/060,874	10/02/97
PCT/US98/20775	Non-provisional of	60/060,833	10/02/97
PCT/US98/20775	Non-provisional of	60/060,884	10/02/97
PCT/US98/20775	Non-provisional of	60/060,880	10/02/97
<u>10/100,683</u>	<u>Continuation-in-part of</u>	<u>09/984,429</u>	10/30/01
09/984,429	Non-provisional of	60/244,591	11/01/00
09/984,429	Continuation-in-part of	09/288,143	04/08/99
09/288,143	Continuation-in-part of	PCT/US98/21142	10/08/98
<u>10/100,683</u>	<u>Non-provisional of</u>	<u>60/244,591</u>	11/01/00
10/100,683	Continuation-in-part of	09/288,143	04/08/99
09/288,143	Continuation-in-part of	PCT/US98/21142	10/08/98
10/100,683	Continuation-in-part of	PCT/US98/21142	10/08/98
PCT/US98/21142	Non-provisional of	60/061,463	10/09/97
PCT/US98/21142	Non-provisional of	60/061,529	10/09/97
PCT/US98/21142	Non-provisional of	60/071,498	10/09/97
PCT/US98/21142	Non-provisional of	60/061,527	10/09/97
PCT/US98/21142	Non-provisional of	60/061,536	10/09/97
PCT/US98/21142	Non-provisional of	60/061,532	10/09/97
<u>10/100,683</u>	<u>Continuation-in-part of</u>	<u>09/296,622</u>	04/23/99
09/296,622	Continuation-in-part of	PCT/US98/22376	10/23/98
10/100,683	Continuation-in-part of	PCT/US98/22376	10/23/98
PCT/US98/22376	Non-provisional of	60/063,099	10/24/97
PCT/US98/22376	Non-provisional of	60/063,088	10/24/97
PCT/US98/22376	Non-provisional of	60/063,100	10/24/97
PCT/US98/22376	Non-provisional of	60/063,387	10/24/97
PCT/US98/22376	Non-provisional of	60/063,148	10/24/97
PCT/US98/22376	Non-provisional of	60/063,386	10/24/97
PCT/US98/22376	Non-provisional of	60/062,784	10/24/97
PCT/US98/22376	Non-provisional of	60/063,091	10/24/97
PCT/US98/22376	Non-provisional of	60/063,090	10/24/97
PCT/US98/22376	Non-provisional of	60/063,089	10/24/97
PCT/US98/22376	Non-provisional of	60/063,092	10/24/97
PCT/US98/22376	Non-provisional of	60/063,111	10/24/97
PCT/US98/22376	Non-provisional of	60/063,101	10/24/97
PCT/US98/22376	Non-provisional of	60/063,109	10/24/97
PCT/US98/22376	Non-provisional of	60/063,110	10/24/97
PCT/US98/22376	Non-provisional of	60/063,098	10/24/97
PCT/US98/22376	Non-provisional of	60/063,097	10/24/97
10/100,683	Continuation-in-part of	09/974,879	10/12/01

09/974,879	Non-provisional of	60/239,893	10/13/00
09/974,879	Continuation-in-part of	09/818,683	03/28/01
09/818,683	Continuation of	09/305,736	05/05/99
09/305,736	Continuation-in-part of	PCT/US98/23435	11/04/98
10/100,683	Continuation-in-part of	09/818,683	03/28/01
09/818,683	Continuation of	09/305,736	05/05/99
09/305,736	Continuation-in-part of	PCT/US98/23435	11/04/98
10/100,683	Continuation-in-part of	09/305,736	05/05/99
09/305,736	Continuation-in-part of	PCT/US98/23435	11/04/98
10/100,683	Continuation-in-part of	PCT/US98/23435	11/04/98
PCT/US98/23435	Non-provisional of	60/064,911	11/07/97
PCT/US98/23435	Non-provisional of	60/064,912	11/07/97
PCT/US98/23435	Non-provisional of	60/064,983	11/07/97
PCT/US98/23435	Non-provisional of	60/064,900	11/07/97
PCT/US98/23435	Non-provisional of	60/064,988	11/07/97
PCT/US98/23435	Non-provisional of	60/064,987	11/07/97
PCT/US98/23435	Non-provisional of	60/064,908	11/07/97
PCT/US98/23435	Non-provisional of	60/064,984	11/07/97
PCT/US98/23435	Non-provisional of	60/064,985	11/07/97
PCT/US98/23435	Non-provisional of	60/066,094	11/17/97
PCT/US98/23435	Non-provisional of	60/066,100	11/17/97
PCT/US98/23435	Non-provisional of	60/066,089	11/17/97
PCT/US98/23435	Non-provisional of	60/066,095	11/17/97
PCT/US98/23435	Non-provisional of	60/066,090	11/17/97
10/100,683	Continuation-in-part of	09/334,595	06/17/99
09/334,595	Continuation-in-part of	PCT/US98/27059	12/17/98
10/100,683	Continuation-in-part of	PCT/US98/27059	12/17/98
PCT/US98/27059	Non-provisional of	60/070,923	12/18/97
PCT/US98/27059	Non-provisional of	60/068,007	12/18/97
PCT/US98/27059	Non-provisional of	60/068,057	12/18/97
PCT/US98/27059	Non-provisional of	60/068,006	12/18/97
PCT/US98/27059	Non-provisional of	60/068,369	12/19/97
PCT/US98/27059	Non-provisional of	60/068,367	12/19/97
PCT/US98/27059	Non-provisional of	60/068,368	12/19/97
PCT/US98/27059	Non-provisional of	60/068,169	12/19/97
PCT/US98/27059	Non-provisional of	60/068,053	12/18/97
PCT/US98/27059	Non-provisional of	60/068,064	12/18/97
PCT/US98/27059	Non-provisional of	60/068,054	12/18/97
PCT/US98/27059	Non-provisional of	60/068,008	12/18/97
PCT/US98/27059	Non-provisional of	60/068,365	12/19/97
10/100,683	Continuation-in-part of	09/938,671	08/27/01
09/938,671	Continuation of	09/739,907	12/20/00
09/739,907	Continuation of	09/348,457	07/07/99
09/348,457	Continuation-in-part of	PCT/US99/00108	01/06/99
10/100,683	Continuation-in-part of	09/739,907	12/20/00
09/739,907	Continuation of	09/348,457	07/07/99
09/348,457	Continuation-in-part of	PCT/US99/00108	01/06/99
10/100,683	Continuation-in-part of	09/348,457	07/07/99
09/348,457	Continuation-in-part of	PCT/US99/00108	01/06/99
10/100,683	Continuation-in-part of	PCT/US99/00108	01/06/99
PCT/US99/00108	Non-provisional of	60/070,704	01/07/98

PCT/US99/00108	Non-provisional of	60/070,658	01/07/98
PCT/US99/00108	Non-provisional of	60/070,692	01/07/98
PCT/US99/00108	Non-provisional of	60/070,657	01/07/98
10/100,683	Continuation-in-part of	09/949,925	09/12/01
09/949,925	Non-provisional of	60/232,150	09/12/00
09/949,925	Continuation-in-part of	PCT/US99/01621	01/27/99
09/949,925	Continuation-in-part of	09/363,044	07/29/99
09/363,044	Continuation-in-part of	PCT/US99/01621	01/27/99
10/100,683	Continuation-in-part of	09/813,153	03/21/01
09/813,153	Continuation of	09/363,044	07/29/99
09/363,044	Continuation-in-part of	PCT/US99/01621	01/27/99
10/100,683	Continuation-in-part of	09/363,044	07/29/99
09/363,044	Continuation-in-part of	PCT/US99/01621	01/27/99
10/100,683	Continuation-in-part of	PCT/US99/01621	01/27/99
PCT/US99/01621	Non-provisional of	60/073,170	01/30/98
PCT/US99/01621	Non-provisional of	60/073,167	01/30/98
PCT/US99/01621	Non-provisional of	60/073,165	01/30/98
PCT/US99/01621	Non-provisional of	60/073,164	01/30/98
PCT/US99/01621	Non-provisional of	60/073,162	01/30/98
PCT/US99/01621	Non-provisional of	60/073,161	01/30/98
PCT/US99/01621	Non-provisional of	60/073,160	01/30/98
PCT/US99/01621	Non-provisional of	60/073,159	01/30/98
10/100,683	Continuation-in-part of	10/062,548	02/05/02
10/062,548	Continuation of	09/369,247	08/05/99
09/369,247	Continuation-in-part of	PCT/US99/02293	02/04/99
10/100,683	Continuation-in-part of	09/369,247	08/05/99
09/369,247	Continuation-in-part of	PCT/US99/02293	02/04/99
10/100,683	Continuation-in-part of	PCT/US99/02293	02/04/99
PCT/US99/02293	Non-provisional of	60/074,118	02/09/98
PCT/US99/02293	Non-provisional of	60/074,157	02/09/98
PCT/US99/02293	Non-provisional of	60/074,037	02/09/98
PCT/US99/02293	Non-provisional of	60/074,141	02/09/98
PCT/US99/02293	Non-provisional of	60/074,341	02/09/98
10/100,683	Continuation-in-part of	09/716,129	11/17/00
09/716,129	Continuation-in-part of	PCT/US99/03939	02/24/99
09/716,129	CON	09/382,572	08/25/99
09/382,572	Continuation-in-part of	PCT/US99/03939	02/24/99
10/100,683	Continuation-in-part of	PCT/US99/03939	02/24/99
PCT/US99/03939	Non-provisional of	60/076,053	02/26/98
PCT/US99/03939	Non-provisional of	60/076,051	02/26/98
PCT/US99/03939	Non-provisional of	60/076,054	02/26/98
PCT/US99/03939	Non-provisional of	60/076,052	02/26/98
PCT/US99/03939	Non-provisional of	60/076,057	02/26/98
10/100,683	Continuation-in-part of	09/798,889	03/06/01
09/798,889	CON	09/393,022	09/09/99
09/393,022	Continuation-in-part of	PCT/US99/05721	03/11/99
10/100,683	Continuation-in-part of	PCT/US99/05721	03/11/99
PCT/US99/05721	Non-provisional of	60/077,714	03/12/98

PCT/US99/05721	Non-provisional of	60/077,686	03/12/98
PCT/US99/05721	Non-provisional of	60/077,687	03/12/98
PCT/US99/05721	Non-provisional of	60/077,696	03/12/98
<u>10/100,683</u>	<u>Continuation-in-part of</u>	<u>09/397,945</u>	09/17/99
09/397,945	Continuation-in-part of	PCT/US99/05804	03/18/99
10/100,683	Continuation-in-part of	PCT/US99/05804	03/18/99
PCT/US99/05804	Non-provisional of	60/078,566	03/19/98
PCT/US99/05804	Non-provisional of	60/078,576	03/19/98
PCT/US99/05804	Non-provisional of	60/078,573	03/19/98
PCT/US99/05804	Non-provisional of	60/078,574	03/19/98
PCT/US99/05804	Non-provisional of	60/078,579	03/19/98
PCT/US99/05804	Non-provisional of	60/080,314	04/01/98
PCT/US99/05804	Non-provisional of	60/080,312	04/01/98
PCT/US99/05804	Non-provisional of	60/078,578	03/19/98
PCT/US99/05804	Non-provisional of	60/078,581	03/19/98
PCT/US99/05804	Non-provisional of	60/078,577	03/19/98
PCT/US99/05804	Non-provisional of	60/078,563	03/19/98
PCT/US99/05804	Non-provisional of	60/080,313	04/01/98
10/100,683	Continuation-in-part of	09/948,783	09/10/01
<u>09/948,783</u>	<u>Non-provisional of</u>	<u>60/231,846</u>	09/11/00
09/948,783	Continuation-in-part of	09/892,877	06/28/01
<u>09/892,877</u>	<u>Continuation of</u>	<u>09/437,658</u>	11/10/99
09/437,658	Continuation-in-part of	PCT/US99/09847	05/06/99
<u>10/100,683</u>	<u>Continuation-in-part of</u>	<u>09/892,877</u>	06/28/01
09/892,877	Continuation of	09/437,658	11/10/99
09/437,658	Continuation-in-part of	PCT/US99/09847	05/06/99
10/100,683	Continuation-in-part of	PCT/US99/09847	05/06/99
PCT/US99/09847	Non-provisional of	60/085,093	05/12/98
PCT/US99/09847	Non-provisional of	60/085,094	05/12/98
PCT/US99/09847	Non-provisional of	60/085,105	05/12/98
PCT/US99/09847	Non-provisional of	60/085,180	05/12/98
PCT/US99/09847	Non-provisional of	60/085,927	05/18/98
PCT/US99/09847	Non-provisional of	60/085,906	05/18/98
PCT/US99/09847	Non-provisional of	60/085,920	05/18/98
PCT/US99/09847	Non-provisional of	60/085,924	05/18/98
PCT/US99/09847	Non-provisional of	60/085,922	05/18/98
PCT/US99/09847	Non-provisional of	60/085,923	05/18/98
PCT/US99/09847	Non-provisional of	60/085,921	05/18/98
PCT/US99/09847	Non-provisional of	60/085,925	05/18/98
PCT/US99/09847	Non-provisional of	60/085,928	05/18/98
10/100,683	Continuation-in-part of	10/050,873	01/18/02
10/050,873	Non-provisional of	60/263,681	01/24/01
10/050,873	Non-provisional of	60/263,230	01/23/01
10/050,873	Continuation-in-part of	09/461,325	12/14/99
09/461,325	Continuation-in-part of	PCT/US99/13418	06/15/99
10/100,683	Continuation-in-part of	10/012,542	12/12/01
10/012,542	Divisional of	09/461,325	12/14/99

09/461,325	Continuation-in-part of	PCT/US99/13418	06/15/99
10/100,683	Continuation-in-part of	09/461,325	12/14/99
09/461,325	Continuation-in-part of	PCT/US99/13418	06/15/99
10/100,683	Continuation-in-part of	PCT/US99/13418	06/15/99
PCT/US99/13418	Non-provisional of	60/089,507	06/16/98
PCT/US99/13418	Non-provisional of	60/089,508	06/16/98
PCT/US99/13418	Non-provisional of	60/089,509	06/16/98
PCT/US99/13418	Non-provisional of	60/089,510	06/16/98
PCT/US99/13418	Non-provisional of	60/090,112	06/22/98
PCT/US99/13418	Non-provisional of	60/090,113	06/22/98
10/100,683	Continuation-in-part of	09/984,271	10/29/01
09/984,271	Divisional of	09/482,273	01/13/00
09/482,273	Continuation-in-part of	PCT/US99/15849	07/14/99
10/100,683	Continuation-in-part of	09/984,276	10/29/01
09/984,276	Divisional of	09/482,273	01/13/00
09/482,273	Continuation-in-part of	PCT/US99/15849	07/14/99
10/100,683	Continuation-in-part of	09/482,273	01/13/00
09/482,273	Continuation-in-part of	PCT/US99/15849	07/14/99
10/100,683	Continuation-in-part of	PCT/US99/15849	07/14/99
PCT/US99/15849	Non-provisional of	60/092,921	07/15/98
PCT/US99/15849	Non-provisional of	60/092,922	07/15/98
PCT/US99/15849	Non-provisional of	60/092,956	07/15/98
10/100,683	Continuation-in-part of	PCT/US01/29871	09/24/01
PCT/US01/29871	Non-provisional of	60/234,925	09/25/00
PCT/US01/29871	Continuation-in-part of	PCT/US01/00911	01/12/01
10/100,683	Continuation-in-part of	PCT/US01/00911	01/12/01
PCT/US01/00911	Continuation-in-part of	09/482,273	01/13/00
10/100,683	Non-provisional of	60/350,898	01/25/02
10/100,683	Continuation-in-part of	09/489,847	01/24/00
09/489,847	Continuation-in-part of	PCT/US99/17130	07/29/99
10/100,683	Continuation-in-part of	PCT/US99/17130	07/29/99
PCT/US99/17130	Non-provisional of	60/094,657	07/30/98
PCT/US99/17130	Non-provisional of	60/095,486	08/05/98
PCT/US99/17130	Non-provisional of	60/096,319	08/12/98
PCT/US99/17130	Non-provisional of	60/095,454	08/06/98
PCT/US99/17130	Non-provisional of	60/095,455	08/06/98
10/100,683	Continuation-in-part of	10/054,988	01/25/02
10/054,988	Continuation of	09/904,615	07/16/01
09/904,615	Continuation of	09/739,254	12/19/00
09/739,254	Continuation of	09/511,554	02/23/00
09/511,554	Continuation-in-part of	PCT/US99/19330	08/24/99
10/100,683	Continuation-in-part of	09/904,615	07/16/01
09/904,615	Continuation of	09/739,254	12/19/00
09/739,254	Continuation of	09/511,554	02/23/00
09/511,554	Continuation-in-part of	PCT/US99/19330	08/24/99
10/100,683	Continuation-in-part of	PCT/US99/19330	08/24/99
PCT/US99/19330	Non-provisional of	60/097,917	08/25/98
PCT/US99/19330	Non-provisional of	60/098,634	08/31/98
10/100,683	Continuation-in-part of	09/820,893	03/30/01
09/820,893	Continuation of	09/531,119	03/20/00
09/531,119	Continuation-in-part of	PCT/US99/22012	09/22/99

10/100,683	Continuation-in-part of	PCT/US99/22012	09/22/99
PCT/US99/22012	Non-provisional of	60/101,546	09/23/98
PCT/US99/22012	Non-provisional of	60/102,895	10/02/98
10/100,683	Continuation-in-part of	09/948,820	09/10/01
09/948,820	Continuation of	09/565,391	05/05/00
09/565,391	Continuation-in-part of	PCT/US99/26409	11/09/99
10/100,683	Continuation-in-part of	09/565,391	05/05/00
09/565,391	Continuation-in-part of	PCT/US99/26409	11/09/99
10/100,683	Continuation-in-part of	PCT/US99/26409	11/09/99
PCT/US99/26409	Non-provisional of	60/108,207	11/12/98
10/100,683	Continuation-in-part of	09/895,298	07/02/01
09/895,298	Continuation of	09/591,316	06/09/00
09/591,316	Continuation-in-part of	PCT/US99/29950	12/16/99
10/100,683	Continuation-in-part of	PCT/US99/29950	12/16/99
PCT/US99/29950	Non-provisional of	60/113,006	12/18/98
PCT/US99/29950	Non-provisional of	60/112,809	12/17/98
10/100,683	Continuation-in-part of	09/985,153	11/01/01
09/985,153	Continuation of	09/618,150	07/17/00
09/618,150	Continuation-in-part of	PCT/US00/00903	01/18/00
10/100,683	Continuation-in-part of	PCT/US00/00903	01/18/00
PCT/US00/00903	Non-provisional of	60/116,330	01/19/99
10/100,683	Continuation-in-part of	09/997,131	11/30/01
09/997,131	Continuation of	09/628,508	07/28/00
09/628,508	Continuation-in-part of	PCT/US00/03062	02/08/00
10/100,683	Continuation-in-part of	PCT/US00/03062	02/08/00
PCT/US00/03062	Non-provisional of	60/119,468	02/10/99
10/100,683	Continuation-in-part of	10/050,882	01/18/02
10/050,882	Continuation of	09/661,453	09/13/00
09/661,453	Continuation-in-part of	PCT/US00/06783	03/16/00
10/100,683	Continuation-in-part of	09/661,453	09/13/00
09/661,453	Continuation-in-part of	PCT/US00/06783	03/16/00
10/100,683	Continuation-in-part of	PCT/US00/06783	03/16/00
PCT/US00/06783	Non-provisional of	60/125,055	03/18/99
10/100,683	Continuation-in-part of	10/050,704	01/18/02
10/050,704	Continuation of	09/684,524	10/10/00
09/684,524	Continuation-in-part of	PCT/US00/08979	04/06/00
10/100,683	Continuation-in-part of	09/684,524	10/10/00
09/684,524	Continuation-in-part of	PCT/US00/08979	04/06/00
10/100,683	Continuation-in-part of	PCT/US00/08979	04/06/00
PCT/US00/08979	Non-provisional of	60/128,693	04/09/99
PCT/US00/08979	Non-provisional of	60/130,991	04/26/99
10/100,683	Continuation-in-part of	10/042,141	01/11/02
10/042,141	Continuation of	09/726,643	12/01/00
09/726,643	Continuation-in-part of	PCT/US00/15187	06/02/00
10/100,683	Continuation-in-part of	09/726,643	12/01/00
09/726,643	Continuation-in-part of	PCT/US00/15187	06/02/00
10/100,683	Continuation-in-part of	PCT/US00/15187	06/02/00
PCT/US00/15187	Non-provisional of	60/137,725	06/07/99
10/100,683	Continuation-in-part of	09/756,168	01/09/01
09/756,168	Continuation-in-part of	PCT/US00/19735	07/23/99
10/100,683	Continuation-in-part of	PCT/US00/19735	07/20/00



PCT/US00/19735	Non-provisional of	60/145,220	07/23/99
10/100,683	Continuation-in-part of	PZ042P1C1	02/01/02
PZ042P1C1	Continuation of	09/781,417	02/13/01
09/781,417	Continuation-in-part of	PCT/US00/22325	08/16/00
10/100,683	Continuation-in-part of	09/781,417	02/13/01
09/781,417	Continuation-in-part of	PCT/US00/22325	08/16/00
10/100,683	Continuation-in-part of	PCT/US00/22325	08/16/00
PCT/US00/22325	Non-provisional of	60/149,182	08/17/99
10/100,683	Continuation-in-part of	09/789,561	02/22/01
09/789,561	Continuation-in-part of	PCT/US00/24008	08/31/00
10/100,683	Continuation-in-part of	PCT/US00/24008	08/31/00
PCT/US00/24008	Non-provisional of	60/152,315	09/03/99
PCT/US00/24008	Non-provisional of	60/152,317	09/03/99
10/100,683	Continuation-in-part of	09/800,729	03/08/01
09/800,729	Continuation-in-part of	PCT/US00/26013	09/22/00
10/100,683	Continuation-in-part of	PCT/US00/26013	09/22/00
PCT/US00/26013	Non-provisional of	60/155,709	09/24/99
10/100,683	Continuation-in-part of	09/832,129	04/11/01
09/832,129	Continuation-in-part of	PCT/US00/28664	10/17/00
10/100,683	Continuation-in-part of	PCT/US00/28664	10/17/00
PCT/US00/28664	Non-provisional of	60/163,085	11/02/99
PCT/US00/28664	Non-provisional of	60/172,411	12/17/99
10/100,683	Continuation-in-part of	PCT/US00/29363	10/25/00
PCT/US00/29363	Non-provisional of	60/215,139	06/30/00
PCT/US00/29363	Non-provisional of	60/162,239	10/29/99
10/100,683	Continuation-in-part of	PCT/US00/29360	10/25/00
PCT/US00/29360	Non-provisional of	60/215,138	06/30/00
PCT/US00/29360	Non-provisional of	60/162,211	10/29/99
10/100,683	Continuation-in-part of	PCT/US00/29362	10/25/00
PCT/US00/29362	Non-provisional of	60/215,131	06/30/00
PCT/US00/29362	Non-provisional of	60/162,240	10/29/99
10/100,683	Continuation-in-part of	PCT/US00/29365	10/25/00
PCT/US00/29365	Non-provisional of	60/219,666	07/21/00
PCT/US00/29365	Non-provisional of	60/162,237	10/29/99
10/100,683	Continuation-in-part of	PCT/US00/29364	10/25/00
PCT/US00/29364	Non-provisional of	60/215,134	06/30/00
PCT/US00/29364	Non-provisional of	60/162,238	10/29/99
10/100,683	Continuation-in-part of	PCT/US00/30040	11/01/00
PCT/US00/30040	Non-provisional of	60/215,130	06/30/00
PCT/US00/30040	Non-provisional of	60/163,580	11/05/99
10/100,683	Continuation-in-part of	PCT/US00/30037	11/01/00
PCT/US00/30037	Non-provisional of	60/215,137	06/30/00
PCT/US00/30037	Non-provisional of	60/163,577	11/05/99
10/100,683	Continuation-in-part of	PCT/US00/30045	11/01/00
PCT/US00/30045	Non-provisional of	60/215,133	06/30/00
PCT/US00/30045	Non-provisional of	60/163,581	11/05/99
10/100,683	Continuation-in-part of	PCT/US00/30036	11/01/00
PCT/US00/30036	Non-provisional of	60/221,366	07/27/00
PCT/US00/30036	Non-provisional of	60/163,576	11/05/99
10/100,683	Continuation-in-part of	PCT/US00/30039	11/01/00
PCT/US00/30039	Non-provisional of	60/221,367	07/27/00
PCT/US00/30039	Non-provisional of	60/195,296	04/07/00
PCT/US00/30039	Non-provisional of	60/164,344	11/09/99

10/100,683	Continuation-in-part of	PCT/US00/30654	11/08/00
PCT/US00/30654	Non-provisional of	60/221,142	07/27/00
PCT/US00/30654	Non-provisional of	60/164,835	11/12/99
10/100,683	Continuation-in-part of	PCT/US00/30628	11/08/00
PCT/US00/30628	Non-provisional of	60/215,140	06/30/00
PCT/US00/30628	Non-provisional of	60/164,744	11/12/99
10/100,683	Continuation-in-part of	PCT/US00/30653	11/08/00
PCT/US00/30653	Non-provisional of	60/221,193	07/27/00
PCT/US00/30653	Non-provisional of	60/164,735	11/12/99
10/100,683	Continuation-in-part of	PCT/US00/30629	11/08/00
PCT/US00/30629	Non-provisional of	60/222,904	08/03/00
PCT/US00/30629	Non-provisional of	60/164,825	11/12/99
10/100,683	Continuation-in-part of	PCT/US00/30679	11/08/00
PCT/US00/30679	Non-provisional of	60/224,007	08/04/00
PCT/US00/30679	Non-provisional of	60/164,834	11/12/99
10/100,683	Continuation-in-part of	PCT/US00/30674	11/08/00
PCT/US00/30674	Non-provisional of	60/215,128	06/30/00
PCT/US00/30674	Non-provisional of	60/164,750	11/12/99
10/100,683	Continuation-in-part of	PCT/US00/31162	11/15/00
60/215,136	Non-provisional of	60/215,136	06/30/00
60/215,136	Non-provisional of	60/166,415	11/19/99
10/100,683	Continuation-in-part of	PCT/US00/31282	11/15/00
PCT/US00/31282	Non-provisional of	60/219,665	07/21/00
PCT/US00/31282	Non-provisional of	60/166,414	11/19/99
10/100,683	Continuation-in-part of	PCT/US00/30657	11/08/00
PCT/US00/30657	Non-provisional of	60/215,132	06/30/00
PCT/US00/30657	Non-provisional of	60/164,731	11/12/99
10/100,683	Continuation-in-part of	PCT/US01/01396	01/17/01
60/256,968	Non-provisional of	60/256,968	12/21/00
60/256,968	Non-provisional of	60/226,280	08/18/00
10/100,683	Continuation-in-part of	PCT/US01/01387	01/17/01
60/259,803	Non-provisional of	60/259,803	01/05/01
60/259,803	Non-provisional of	60/226,380	08/18/00
10/100,683	Continuation-in-part of	PCT/US01/01567	01/17/01
PCT/US01/01567	Non-provisional of	60/228,084	08/28/00
10/100,683	Continuation-in-part of	PCT/US01/01431	01/17/01
PCT/US01/01431	Non-provisional of	60/231,968	09/12/00
PCT/US01/01431	Continuation-in-part of	09/915,582	07/27/01
10/100,683	Continuation-in-part of	PCT/US01/01432	01/17/01
PCT/US01/01432	Non-provisional of	60/236,326	09/29/00
10/100,683	Continuation-in-part of	PCT/US01/00544	01/09/01
PCT/US01/00544	Non-provisional of	60/234,211	09/20/00
10/100,683	Continuation-in-part of	PCT/US01/01435	01/17/01
PCT/US01/01435	Non-provisional of	60/226,282	08/18/00
10/100,683	Continuation-in-part of	PCT/US01/01386	01/17/01
PCT/US01/01386	Non-provisional of	60/232,104	09/12/00
10/100,683	Continuation-in-part of	PCT/US01/01565	01/17/01
PCT/US01/01565	Non-provisional of	60/234,210	09/20/00
10/100,683	Continuation-in-part of	PCT/US01/01394	01/17/01
PCT/US01/01394	Non-provisional of	60/259,805	01/05/01
PCT/US01/01394	Non-provisional of	60/226,278	08/18/00
10/100,683	Continuation-in-part of	PCT/US01/01434	01/17/01
PCT/US01/01434	Non-provisional of	60/259,678	01/05/01

PCT/US01/01434	Non-provisional of	60/226,279	08/18/00
10/100,683	Continuation-in-part of	PCT/US01/01397	01/17/01
PCT/US01/01397	Non-provisional of	60/226,281	08/18/00
10/100,683	Continuation-in-part of	PCT/US01/01385	01/17/01
PCT/US01/01385	Non-provisional of	60/231,969	09/12/00
10/100,683	Continuation-in-part of	PCT/US01/01384	01/17/01
PCT/US01/01384	Non-provisional of	60/259,516	01/04/01
PCT/US01/01384	Non-provisional of	60/228,086	08/28/00
10/100,683	Continuation-in-part of	PCT/US01/01383	01/17/01
PCT/US01/01383	Non-provisional of	60/259,804	01/05/01
PCT/US01/01383	Non-provisional of	60/228,083	08/28/00
10/100,683	Continuation-in-part of	PCT/US02/05064	02/21/02
PCT/US02/05064	Non-provisional of	60/304,444	07/12/01
PCT/US02/05064	Non-provisional of	60/270,658	02/23/01
10/100,683	Continuation-in-part of	PCT/US02/05301	02/21/02
PCT/US02/05301	Non-provisional of	60/304,417	07/12/01
PCT/US02/05301	Non-provisional of	60/270,625	02/23/01
10/100,683	Non-provisional of	60/304,121	07/11/01
10/100,683	Non-provisional of	60/295,869	06/06/01
10/100,683	Non-provisional of	60/325,209	09/28/01
10/100,683	Non-provisional of	60/311,085	08/10/01
10/100,683	Non-provisional of	60/330,629	10/26/01
10/100,683	Non-provisional of	60/331,046	11/07/01
10/100,683	Non-provisional of	60/358,554	02/22/02
10/100,683	Non-provisional of	60/358,714	02/25/02

; wherein each of the above applications are all herein incorporated by reference in their entirety.

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### ***Field of the Invention***

The present invention relates to human secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus and conditions related thereto. Antibodies that bind these polypeptides are also encompassed by the present invention. Also encompassed by the invention are vectors, host cells, and recombinant and synthetic methods for producing said polynucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

### ***Background of the Invention***

Over the past few decades, an increasing percentage of the population has become diabetic. Diabetes mellitus is categorized into two types: Type I, known as Insulin-Dependent

Diabetes Mellitus (IDDM), or Type II, known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM). IDDM is an autoimmune disorder in which the insulin-secreting pancreatic beta cells of the islets of Langerhans are destroyed. In these individuals, recombinant insulin therapy is employed to maintain glucose homeostasis and normal energy metabolism. NIDDM, on the other hand, is a polygenic disorder with no one gene responsible for the progression of the disease.

In NIDDM, insulin resistance eventually leads to the abolishment of insulin secretion resulting in insulin deficiency. Insulin resistance, at least in part, ensues from a block at the level of glucose uptake and phosphorylation in humans. Diabetics demonstrate a decrease in expression in adipose tissue of insulin-receptor substrate 1 (“IRS1”) (Carvalho et al., FASEB J 13(15):2173-8 (1999)), glucose transporter 4 (“GLUT4”) (Garvey et al., Diabetes 41(4):465-75 (1992)), and the novel abundant protein M gene transcript 1 (“apM1”) (Statnick et al., Int J Exp Diabetes 1(2): 81-8 (2000)), as well as other as of yet unidentified factors. Insulin deficiency in NIDDM leads to failure of normal pancreatic beta-cell function and eventually to pancreatic-beta cell death.

Insulin affects fat, muscle, and liver. Insulin is the major regulator of energy metabolism. Malfunctioning of any step(s) in insulin secretion and/or action can lead to many disorders, including for example the dysregulation of oxygen utilization, adipogenesis, glycogenesis, lipogenesis, glucose uptake, protein synthesis, thermogenesis, and maintenance of the basal metabolic rate. This malfunctioning results in diseases and/or disorders that include, but are not limited to, hyperinsulinemia, insulin resistance, insulin deficiency, hyperglycemia, hyperlipidemia, hyperketonemia, and diabetes.

Numerous debilitating diabetes-related secondary effects include, but are not limited to, obesity, forms of blindness (cataracts and diabetic retinopathy), limb amputations, kidney failure, fatty liver, coronary artery disease, and neuropathy.

Some of the current drugs used to treat insulin resistance and/or diabetes (e.g., insulin secretagogues – sulfonylurea, insulin sensitizers – thiazolidenediones and metformin, and alpha-glucosidase and lipase inhibitors) are inadequate due to the dosage amounts and frequency with which they have to be administered as a result of poor pharmacokinetic properties, the lack of effective control over blood sugar levels, and potential side effects, among other reasons. Diabetes Therapeutic proteins in their native state or when recombinantly produced exhibit a rapid *in vivo* clearance. Typically, significant amounts of therapeutics are required to be effective during therapy. In addition, small molecules smaller than the 20 kDa range can be readily filtered through the renal tubules (glomerulus) leading to dose-dependent nephrotoxicity. Therefore, there is a need for improvement in treatment (e.g., a need for prolonging the effects of therapeutics of diabetes and/or diabetes related conditions).

### ***Summary of the Invention***

The present invention encompasses human secreted proteins/polypeptides, and isolated nucleic acid molecules encoding said proteins/polypeptides, useful for detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus and conditions related thereto. Antibodies that bind these polypeptides are also encompassed by the present invention; as are vectors, host cells, and recombinant and synthetic methods for producing said polynucleotides, polypeptides, and/or antibodies. The invention further encompasses screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention also encompasses methods and compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

## ***Detailed Description***

### **Polynucleotides and Polypeptides of the Invention**

#### **Description of Table 1A**

Table 1A summarizes information concerning certain polynucleotides and polypeptides of the invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCC Deposit No:Z and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column, the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh column) and the "3' NT of Clone Seq." (eighth column) of SEQ ID NO:X. In the ninth column, the nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, in column ten, the nucleotide position of SEQ ID NO:X of the

predicted signal sequence is identified as "5' NT of First AA of Signal Pep." In the eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF".

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1A and/or elsewhere herein

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1A. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

Also provided in Table 1A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the

sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC Deposit No.Z.

5 The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC deposit No.Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA contained in  
10 ATCC Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC Deposit No.Z.

#### 15 **Description of Table 1B (Comprised of Tables 1B.1 and 1B.2)**

Table 1B.1 and Table 1B.2 summarize some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID:), contig sequences (contig identifier (Contig ID:)) and contig nucleotide sequence identifiers (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded  
20 thereby. The first column of Tables 1B.1 and 1B.2 provide the gene numbers in the application for each clone identifier. The second column of Tables 1B.1 and 1B.2 provide unique clone identifiers, "Clone ID:", for cDNA clones related to each contig sequence disclosed in Table 1A and/or Table 1B. The third column of Tables 1B.1 and 1B.2 provide unique contig identifiers, "Contig ID:" for each of the contig sequences disclosed in these tables. The fourth column of  
25 Tables 1B.1 and 1B.2 provide the sequence identifiers, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1A and/or 1B.

##### **Table 1B.1**

The fifth column of Table 1B.1, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineates  
30 the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1B.1 as SEQ ID NO:Y (column 6). Column 7 of Table 1B.1 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988));  
35 specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group



(GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1B.1 as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1B.1. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 8 of Table 1B.1 ("Tissue Distribution") is described below in Table 1B.2 Column 5. Column 9 of Table 1B.1 ("Cytologic Band") provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in Table 1B.1, column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

### Table 1B.2

Column 5 of Table 1B.2, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first code number shown in Table 1B.2 column 5 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. The second number in column 5 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the corresponding tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of <sup>33</sup>P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL)

which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after “[array code]:” represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

#### **Description of Table 1C**

Table 1C summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID:), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, “Clone ID:”, for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, “SEQ ID NO:X”, for each contig sequence. The third column provides a unique contig identifier, “Contig ID:” for each contig sequence. The fourth column, provides a BAC identifier “BAC ID NO:A” for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, “SEQ ID NO:B” for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, “Exon From-To”, provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

#### **Description of Table 1D**

Table 1D: In preferred embodiments, the present invention encompasses a method of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; comprising administering to a patient in which such treatment, prevention, or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) represented by Table 1A, Table 1B, and Table 1C, in an amount effective to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate the disease or disorder.

As indicated in Table 1D, the polynucleotides, polypeptides, agonists, or antagonists of the present invention (including antibodies) can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity.

Thus, the polynucleotides or polypeptides, or agonists or antagonists thereof (including antibodies) could be used to treat the associated disease.

Table 1D provides information related to biological activities for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information related to assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID:") provides the unique clone identifier for each clone as previously described and indicated in Tables 1A, 1B, and 1C. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, 1B, and 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity. Table 1D describes the use of FMAT technology, *inter alia*, for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT) is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound fluorophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. *See*, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using fluorometric microvolume assay technology," Journal of Biomolecular Screening; 4:193-204 (1999). In particular, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)).

Table 1D also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction

pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK, ERK, and p38 Kinase Activities" Biol. Chem. 379(8-9): 1101-1110 (1998).

## 10           **Description of Table 1E**

Polynucleotides encoding polypeptides of the present invention can be used in assays to test for one or more biological activities. One such biological activity which may be tested includes the ability of polynucleotides and polypeptides of the invention to stimulate up-regulation or down-regulation of expression of particular genes and proteins. Hence, if polynucleotides and polypeptides of the present invention exhibit activity in altering particular gene and protein expression patterns, it is likely that these polynucleotides and polypeptides of the present invention may be involved in, or capable of effecting changes in, diseases associated with the altered gene and protein expression profiles. Hence, polynucleotides, polypeptides, or antibodies of the present invention could be used to treat said associated diseases.

TaqMan® assays may be performed to assess the ability of polynucleotides (and polypeptides they encode) to alter the expression pattern of particular "target" genes. TaqMan® reactions are performed to evaluate the ability of a test agent to induce or repress expression of specific genes in different cell types. TaqMan® gene expression quantification assays ("TaqMan® assays") are well known to, and routinely performed by, those of ordinary skill in the art. TaqMan® assays are performed in a two step reverse transcription / polymerase chain reaction (RT-PCR). In the first (RT) step, cDNA is reverse transcribed from total RNA samples using random hexamer primers. In the second (PCR) step, PCR products are synthesized from the cDNA using gene specific primers.

To quantify gene expression the Taqman® PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold® DNA Polymerase to cleave a Taqman® probe (distinct from the primers) during PCR. The Taqman® probe contains a reporter dye at the 5'-end of the probe and a quencher dye at the 3' end of the probe. When the probe is intact, the

proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of interest is present, the probe specifically anneals between the forward and reverse primer sites. AmpliTaq Fold DNA Polymerase then cleaves the probe between the reporter and quencher when the probe hybridizes to the target, resulting in increased fluorescence of the reporter (see Figure 2). Accumulation of PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye.

After the probe fragments are displaced from the target, polymerization of the strand continues. The 3'-end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. The increase in fluorescence signal is detected only if the target sequence is complementary to the probe and is amplified during PCR. Because of these requirements, any nonspecific amplification is not detected.

For test sample preparation, vector controls or constructs containing the coding sequence for the gene of interest are transfected into cells, such as for example 293T cells, and supernatants collected after 48 hours. For cell treatment and RNA isolation, multiple primary human cells or human cell lines are used; such cells may include but are not limited to, Normal Human Dermal Fibroblasts, Aortic Smooth Muscle, Human Umbilical Vein Endothelial Cells, HepG2, Daudi, Jurkat, U937, Caco, and THP-1 cell lines. Cells are plated in growth media and growth is arrested by culturing without media change for 3 days, or by switching cells to low serum media and incubating overnight. Cells are treated for 1, 6, or 24 hours with either vector control supernatant or sample supernatant (or purified/partially purified protein preparations in buffer). Total RNA is isolated; for example, by using Trizol extraction or by using the Ambion RNeasy(RN) Spin Kit. RNA isolation system. Expression levels of multiple genes are analyzed using TAQMAN, and expression in the test sample is compared to control vector samples to identify genes induced or repressed. Each of the above described techniques are well known to, and routinely performed by, those of ordinary skill in the art.

Table 1E indicates particular disease classes and preferred indications for which polynucleotides, polypeptides, or antibodies of the present invention may be used in detecting, diagnosing, preventing, treating and/or ameliorating said diseases and disorders based on "target" gene expression patterns which may be up- or down-regulated by polynucleotides (and the encoded polypeptides) corresponding to each indicated cDNA Clone ID (shown in Table 1E, Column 2).

Thus, in preferred embodiments, the present invention encompasses a method of detecting, diagnosing, preventing, treating, and/or ameliorating a disease or disorder listed in the "Disease Class" and/or "Preferred Indication" columns of Table 1E; comprising administering to a patient in which such detection, diagnosis, prevention, or treatment is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, diagnose, prevent, treat, or ameliorate the disease or disorder. The first and second columns of Table 1D show the "Gene No." and "cDNA Clone ID No.", respectively, indicating certain nucleic acids and proteins (or antibodies against the same) of the invention (including polynucleotide, polypeptide, and antibody fragments or variants thereof) that may be used in detecting, diagnosing, preventing, treating, or ameliorating the disease(s) or disorder(s) indicated in the corresponding row in the "Disease Class" or "Preferred Indication" Columns of Table 1E.

In another embodiment, the present invention also encompasses methods of detecting, diagnosing, preventing, treating, or ameliorating a disease or disorder listed in the "Disease Class" or "Preferred Indication" Columns of Table 1E; comprising administering to a patient combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in the "Disease Class" or "Preferred Indication" Columns of Table 1E.

The "Disease Class" Column of Table 1E provides a categorized descriptive heading for diseases, disorders, and/or conditions (more fully described below) that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

The "Preferred Indication" Column of Table 1E describes diseases, disorders, and/or conditions that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

The "Cell Line" and "Exemplary Targets" Columns of Table 1E indicate particular cell lines and target genes, respectively, which may show altered gene expression patterns (i.e., up- or down-regulation of the indicated target gene) in Taqman assays, performed as described above, utilizing polynucleotides of the cDNA Clone ID shown in the corresponding row. Alteration of expression patterns of the indicated "Exemplary Target" genes is correlated with a particular "Disease Class" and/or "Preferred Indication" as shown in the corresponding row under the respective column headings.

The "Exemplary Accessions" Column indicates GenBank Accessions (available online through the National Center for Biotechnology Information (NCBI) at

<http://www.ncbi.nlm.nih.gov/>) which correspond to the "Exemplary Targets" shown in the adjacent row.

The recitation of "Cancer" in the "Disease Class" Column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or  
5 fragment or variant thereof) may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate neoplastic diseases and/or disorders (e.g., leukemias, cancers, etc., as described below under "Hyperproliferative Disorders").

The recitation of "Immune" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or  
10 fragment or variant thereof), may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity" "Cardiovascular Disorders" and/or "Blood-Related Disorders"), and infections (e.g., as described below under "Infectious Disease").

The recitation of "Angiogenesis" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), diseases and/or disorders of the  
20 cardiovascular system (e.g., as described below under "Cardiovascular Disorders"), diseases and/or disorders involving cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level"), diseases and/or disorders involving angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity"), to promote or inhibit cell or tissue regeneration (e.g., as described below under "Regeneration"), or to  
25 promote wound healing (e.g., as described below under "Wound Healing and Epithelial Cell Proliferation").

The recitation of "Diabetes" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent,  
30 and/or ameliorate diabetes (including diabetes mellitus types I and II), as well as diseases and/or disorders associated with, or consequential to, diabetes (e.g. as described below under "Endocrine Disorders," "Renal Disorders," and "Gastrointestinal Disorders").

### **Description of Table 2**

Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID:", corresponding to a cDNA clone disclosed in Table 1A or Table 1B. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1B and allowing for correlation with the information in Table 1B. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth columns. In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

### **Description of Table 3**

Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1B. The second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1A and/or Table 1B. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1B. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In



further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

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#### **Description of Table 4**

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B.2, column 5. Column 1 provides the tissue/cell source identifier code disclosed in Table 1B.2, Column 5. Columns 2-5 provide a description of the tissue or cell source. Note that "Description" and "Tissue" sources (i.e. columns 2 and 3) having the prefix "a\_" indicates organs, tissues, or cells derived from "adult" sources. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease." The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

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#### **Description of Table 5**

Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1B.1, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B.1, column 8, as determined using the Morbid Map database.

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#### **Description of Table 6**

Table 6 summarizes some of the ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application. These deposits were made in addition to those described in the Table 1A.

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#### **Description of Table 7**

Table 7 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

The first column shows the first four letters indicating the Library from which each library clone was derived. The second column indicates the catalogued tissue description for the corresponding libraries. The third column indicates the vector containing the corresponding clones. The fourth column shows the ATCC deposit designation for each library clone as indicated by the deposit information in Table 6.

### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof (e.g., the polypeptide delineated in columns fourteen and fifteen of Table 1A); a nucleic acid sequence contained in SEQ ID NO:X (as described in column 5 of Table 1A and/or column 3 of Table 1B) or the complement thereof; a cDNA sequence contained in Clone ID: (as described in column 2 of Table 1A and/or Table 1B and contained within a library deposited with the ATCC); a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 (EXON From-To) of Table 1C or a fragment or variant thereof; or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complement thereof. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains,

and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

5 In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1B, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID:). Each Clone  
10 ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Table 7 provides a list of the deposited cDNA libraries. One can use the Clone ID: to determine the library source by reference to Tables 6 and 7. Table 7 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone (Clone ID) isolated  
15 from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1A and/or Table 1B correlates the Clone ID names with SEQ ID NO:X. Thus, starting with an SEQ ID NO:X, one can use Tables 1A, 1B, 6, 7, and 9 to determine the corresponding Clone ID, which library it came from and which ATCC deposit the library is contained in. Furthermore, it is possible to retrieve a given cDNA clone from the source library by  
20 techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

In specific embodiments, the polynucleotides of the invention are at least 15, at least  
25 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding  
30 sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ  
35 ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 7 and 8 of Table 1A or the complement thereof, the polynucleotide sequence delineated in

columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID: (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of cDNA clones deposited with the ATCC, described herein), and/or the polynucleotide sequence delineated in column 6 of Table 1C or the complement thereof. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such as any 3' terminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a

mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a polynucleotide sequence described in column 5 of Table 1A, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 10 of Table 1A. SEQ ID NO:X is identified by an integer specified in column 6 of Table 1A. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:2 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:3, and so on.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-

ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of  
5 pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E.  
10 Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

"SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables  
15 1A, Table 1B, or Table 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 11 of Table 1A and or of Table 1B. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1B. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID:" refers to a cDNA clone described in column 2 of Table 1A and/or 1B.

20 "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity (e.g. activity useful in treating, preventing and/or ameliorating diabetes mellitus), antigenicity (ability to bind [or compete with a polypeptide for binding] to an anti-polypeptide antibody), immunogenicity (ability  
25 to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein.  
30 Specifically, one of skill in the art may routinely assay secreted polypeptides (including fragments and variants) of the invention for activity using assays as described in the examples section below.

"A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose  
35 dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit

greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

## 5     **TABLES**

### **Table 1A**

Table 1A summarizes information concerning certain polynucleotides and polypeptides of the invention. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID:", for a  
10     cDNA clone related to each contig sequence disclosed in Table 1A. Third column, the cDNA Clones identified in the second column were deposited as indicated in the third column (i.e. by ATCC Deposit No:Z and deposit date). Some of the deposits contain multiple different clones corresponding to the same gene. In the fourth column, "Vector" refers to the type of vector contained in the corresponding cDNA Clone identified in the second column. In the fifth column,  
15     the nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the corresponding cDNA clone identified in the second column and, in some cases, from additional related cDNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as  
20     SEQ ID NO:X. In the sixth column, "Total NT Seq." refers to the total number of nucleotides in the contig sequence identified as SEQ ID NO:X." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." (seventh column) and the "3' NT of Clone Seq." (eighth column) of SEQ ID NO:X. In the ninth column, the nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as  
25     "5' NT of Start Codon." Similarly, in column ten, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep." In the eleventh column, the translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be routinely translated using known molecular biology techniques. The polypeptides produced by these alternative open reading  
30     frames are specifically contemplated by the present invention.

In the twelfth and thirteenth columns of Table 1A, the first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." In the fourteenth column, the predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion". The amino  
35     acid position of SEQ ID NO:Y of the last amino acid encoded by the open reading frame is identified in the fifteenth column as "Last AA of ORF".

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1A and/or elsewhere herein

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1A. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods

The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

Also provided in Table 1A is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc.,



11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene

5            Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance  
10           gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

15           The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited cDNA (cDNA Clone ID). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

20           Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X and SEQ ID NO:Y using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or  
25           species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

             The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or a cDNA contained in ATCC Deposit No.Z.  
30           The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by a cDNA contained in ATCC deposit No.Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA contained in  
35           ATCC Deposit No.Z, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the

nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA contained in ATCC Deposit No.Z.

Table 1A

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	H2CBU83	209889 05/22/98	pBluescript SK-	11	2703	1	2703	157	157	395	1	30	31	207
1	H2CBU83	209889 05/22/98	pBluescript SK-	259	2709	1	2709	157	157	643	1	30	31	51
2	H6EDC19	209324 10/02/97	Uni-ZAP XR	12	760	324	760	389	389	396	1	25	26	114
3	HACBD91	209626 02/12/98	Uni-ZAP XR	13	1445	1	1445	117	117	397	1	42	43	49
4	HACCI17	203071 07/27/98	Uni-ZAP XR	14	1722	336	1714	461	461	398	1	24	25	218
4	HACCI17	203071 07/27/98	Uni-ZAP XR	260	1380	12	1380	135	135	644	1	24	25	72
5	HAGAQ26	209368 10/16/97	Uni-ZAP XR	15	1333	157	1333	251	251	399	1	20	21	62
6	HAGDS35	209299 09/25/97	Uni-ZAP XR	16	751	1	751	45	45	400	1	23	24	122
6	HAGDS35	209299 09/25/97	Uni-ZAP XR	261	813	1	813	52	52	645	1	23	24	118
7	HAGFI62	209782 04/20/98	Uni-ZAP XR	17	1003	368	992	429	429	401	1	28	29	91
8	HAHDB16	209626 02/12/98	Uni-ZAP XR	18	796	1	796	93	93	402	1	20	21	50
9	HAICP19	209009 04/28/97	Uni-ZAP XR	19	1624	89	1483	128	128	403	1	18	19	446

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
10	HAIFL18	209852 05/07/98	Uni-ZAP XR	20	879	1	879	274	274	404	1	29	30	140
11	HAJAN23	PTA-322 07/09/99	pCMVSPORT 3.0	21	2849	1	2849	109	109	405	1	15	16	563
11	HAJAN23	PTA-322 07/09/99	pCMVSPORT 3.0	262	2288	1	2288	120	120	646	1	15	16	169
12	HAJBR69	209626 02/12/98	pCMVSPORT 3.0	22	755	1	755	262	262	406	1	19	20	53
13	HAMFE15	203364 10/19/98	pCMVSPORT 3.0	23	4129	1	4129	1495	1495	407	1	34	35	421
13	HAMFE15	203364 10/19/98	pCMVSPORT 3.0	263	3758	1	3758	226	226	647	1	23	24	47
14	HAMGR28	209965 06/11/98	pCMVSPORT 3.0	24	1674	47	1674	98	98	408	1	18	19	242
14	HAMGR28	209965 06/11/98	pCMVSPORT 3.0	264	1534	1	1534	40	40	648	1	18	19	203
15	HAPBS03	209651 03/04/98	Uni-ZAP XR	25	1503	45	1479	252	252	409	1	28	29	41
16	HAPNY94	209889 05/22/98	Uni-ZAP XR	26	742	1	742	94	94	410	1	29	30	50
17	HAPOM49	209878 05/18/98	Uni-ZAP XR	27	2005	1	2005	251	251	411	1	22	23	189
17	HAPOM49	209878 05/18/98	Uni-ZAP XR	265	2664	1	2664	448	448	649	1	1	2	123
18	HAPUC89	203570 01/11/99	Uni-ZAP XR	28	1153	1	1153	385	385	412	1	25	26	140

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
19	HATBR65	209626 02/12/98	Uni-ZAP XR	29	812	1	812	252	252	413	1	16	17	64
20	HAUAI83	209626 02/12/98	Uni-ZAP XR	30	910	1	886	253	253	414	1	18	19	49
20	HAUAI83	209626 02/12/98	Uni-ZAP XR	266	1076	1	1076		575	650	1	10	11	23
21	HBAMB15	209683 03/20/98	pSport1	31	821	330	821	390	390	415	1	19	20	59
22	HBGBA69	209878 05/18/98	Uni-ZAP XR	32	981	1	981	124	124	416	1	38	39	240
22	HBGBA69	209878 05/18/98	Uni-ZAP XR	267	943	1	933	62	62	651	1	38	39	60
23	HBGNU56	PTA-2073 06/09/00	Uni-ZAP XR	33	864	1	864	125	125	417	1	21	22	185
23	HBGNU56	PTA-2073 06/09/00	Uni-ZAP XR	268	941	1	941	79	79	652	1	21	22	178
23	HBGNU56	PTA-2073 06/09/00	Uni-ZAP XR	269	988	804	853		2	653	1	1	2	219
24	HBIAE26	209224 08/28/97	Uni-ZAP XR	34	1038	1	1038	75	75	418	1	18	19	39
25	HBINS58	PTA-885 10/28/99	pCMVSPORT 3.0	35	843	1	843	57	57	419	1	30	31	174
25	HBINS58	PTA-885 10/28/99	pCMVSPORT 3.0	270	1566	1	1566	71	71	654	1	29	30	173
25	HBINS58	PTA-885 10/28/99	pCMVSPORT 3.0	271	1067	1	1067	100	100	655	1	29	30	210

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
26	HBJFU48	209125 06/19/97	Uni-ZAP XR	36	849	1	849	20	20	420	1	39	40	40
27	HBJLC01	209651 03/04/98	Uni-ZAP XR	37	872	1	872	87	87	421	1	34	35	46
28	HBNAW17	209242 09/12/97	Uni-ZAP XR	38	601	1	601	77	77	422	1	37	38	61
29	HCE2F54	209626 02/12/98	Uni-ZAP XR	39	1276	19	1256	166	166	423	1	19	20	319
30	HCE3G69	209878 05/18/98	Uni-ZAP XR	40	2084	1	2084	165	165	424	1	19	20	336
30	HCE3G69	209878 05/18/98	Uni-ZAP XR	272	2078	1	2078	165	165	656	1	19	20	105
31	HCE5F43	209580 01/14/98	Uni-ZAP XR	41	1765	1	1765	113	113	425	1	20	21	272
32	HCEFB80	PTA-2069 06/09/00	Uni-ZAP XR	42	2494	1	2494	12	12	426	1	35	36	89
32	HCEFB80	PTA-2069 06/09/00	Uni-ZAP XR	273	2494	1	2451	5	5	657	1	35	36	89
33	HCENK38	209651 03/04/98	Uni-ZAP XR	43	1509	1	1509	10	10	427	1	28	29	52
34	HCEWE20	209300 09/25/97	Uni-ZAP XR	44	885	13	885	166	166	428	1	18	19	51
35	HCFOM18	209324 10/02/97	pSport1	45	639	1	639	28	28	429	1	20	21	63
36	HCGMD59	209627 02/12/98	pCMVSPORT 2.0	46	790	1	780	438	438	430	1	30	31	74

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
37	HCNDR47	PTA-855 10/18/99	Lambda ZAP II	47	1343	1	1343	21	21	431	1	24	25	127
37	HCNDR47	PTA-855 10/18/99	Lambda ZAP II	274	845	1	845	124	124	658	1	47	48	127
37	HCNDR47	PTA-855 10/18/99	Lambda ZAP II	275	738	1	738		603	659	1	8	9	9
38	HCNSB61	209242 09/12/97	pBluescript	48	712	1	712	218	218	432	1	21	22	43
39	HCQCT05	PTA-884 10/28/99	Lambda ZAP II	49	679	1	679		381	433	1			2
39	HCQCT05	PTA-884 10/28/99	Lambda ZAP II	276	2333	1324	2333		1702	660	1			2
40	HCUGM86	PTA-1544 03/21/00	ZAP Express	50	627	1	627	91	91	434	1	24	25	44
41	HCUIM65	209324 10/02/97	ZAP Express	51	875	331	736	557	557	435	1	27	28	47
42	HCWDS72	209852 05/07/98	ZAP Express	52	320	1	320	19	19	436	1	17	18	100
43	HCWKC15	209324 10/02/97	ZAP Express	53	710	1	710	37	37	437	1	18	19	40
44	HCWUM50	209627 02/12/98	ZAP Express	54	1428	208	1428	270	270	438	1	30	31	45
45	HDABR72	209965 06/11/98	pSport1	55	1691	1	1691	33	33	439	1	29	30	146
45	HDABR72	209965 06/11/98	pSport1	277	1746	1	1746	28	28	661	1	29	30	146

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
46	HDPBA28	PTA-163 06/01/99	pCMVSPORT 3.0	56	3447	197	3447	259	259	440	1	32	33	941
46	HDPBA28	PTA-163 06/01/99	pCMVSPORT 3.0	278	4909	1	4909	69	69	662	1	32	33	941
47	HDPBI32	209853 05/07/98	pCMVSPORT 3.0	57	1513	1	1513	37	37	441	1	315	316	316
47	HDPBI32	209853 05/07/98	pCMVSPORT 3.0	279	1579	598	1184	103	103	663	1	30	31	271
47	HDPBI32	209853 05/07/98	pCMVSPORT 3.0	280	587	1	587	51	51	664	1	35	36	138
48	HDPCJ91	209877 05/18/98	pCMVSPORT 3.0	58	6107	1	6107	131	131	442	1	28	29	51
49	HDPCCL63	PTA-1544 03/21/00	pCMVSPORT 3.0	59	3037	115	3037	35	35	443	1	58	59	267
49	HDPCCL63	PTA-1544 03/21/00	pCMVSPORT 3.0	281	2921	1	2921	260	260	665	1	17	18	157
49	HDPCCL63	PTA-1544 03/21/00	pCMVSPORT 3.0	282	1259	358	1259		605	666	1	6	7	118
50	HDPCO25	209125 06/19/97	pCMVSPORT 3.0	60	767	76	767	182	182	444	1	20	21	53
51	HDPGT01	203027 06/26/98	pCMVSPORT 3.0	61	2687	138	2687	8	8	445	1	28	29	87
52	HDPHI51	209125 06/19/97	pCMVSPORT 3.0	62	728	1	728	245	245	446	1	30	31	40
53	HDPIJM30	209563 12/18/97	pCMVSPORT 3.0	63	1635	308	1633	59	59	447	1	59	60	525



Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
53	HDPIJM30	209563 12/18/97	pCMVSPORT 3.0	283	1314	1	1313	259	259	667	1	20	21	59
54	HDPND46	209627 02/12/98	pCMVSPORT 3.0	64	1727	1	1727	15	15	448	1	22	23	484
55	HDPOJ08	209878 05/18/98	pCMVSPORT 3.0	65	1655	1	1655	159	159	449	1	18	19	122
56	HDPPN86	PTA-867 10/26/99	pCMVSPORT 3.0	66	6297	1	6297	127	127	450	1	32	33	46
56	HDPPN86	PTA-867 10/26/99	pCMVSPORT 3.0	284	2042	1	2042	117	117	668	1	26	27	46
57	HDPSB18	PTA-868 10/26/99	pCMVSPORT 3.0	67	3408	1	3408	123	123	451	1	18	19	66
57	HDPSB18	PTA-868 10/26/99	pCMVSPORT 3.0	285	308	1	308		116	669	1	17	18	64
57	HDPSB18	PTA-868 10/26/99	pCMVSPORT 3.0	286	1568	1	1568		1525	670	1	7	8	14
57	HDPSB18	PTA-868 10/26/99	pCMVSPORT 3.0	287	865	1	865		345	671	1	1	2	107
58	HDPSH53	PTA-868 10/26/99	pCMVSPORT 3.0	68	1663	1	1663	158	158	452	1	19	20	90
58	HDPSH53	PTA-868 10/26/99	pCMVSPORT 3.0	288	1687	1	1687	153	153	672	1	19	20	127
58	HDPSH53	PTA-868 10/26/99	pCMVSPORT 3.0	289	570	1	570	212	212	673	1	19	20	90
59	HDPSP01	209745 04/07/98	pCMVSPORT 3.0	69	2343	1	2343	184	184	453	1	20	21	710

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
59	HDPSP01	209745 04/07/98	pCMVSPORT 3.0	290	1752	1	1752	227	227	674	1	20	21	308
60	HDPSP54	209782 04/20/98	pCMVSPORT 3.0	70	3091	2304	3091	2356	2356	454	1	18	19	48
60	HDPSP54	209782 04/20/98	pCMVSPORT 3.0	291	536	1	536	179	179	675	1	41	42	55
61	HDPUH26	PTA-163 06/01/99	pCMVSPORT 3.0	71	2916	1	2916	90	90	455	1	18	19	549
62	HDPWU68	203331 10/08/98	pCMVSPORT 3.0	72	1748	1	1748	40	40	456	1	18	19	467
63	HDPWU34	209782 04/20/98	pCMVSPORT 3.0	73	1277	860	1277	117	117	457	1	23	24	325
63	HDPWU34	209782 04/20/98	pCMVSPORT 3.0	292	427	1	427	111	111	676	1	16	17	44
64	HDPXY01	PTA-868 10/26/99	pCMVSPORT 3.0	74	766	1	766	23	23	458	1	37	38	98
64	HDPXY01	PTA-868 10/26/99	pCMVSPORT 3.0	293	2409	1	2409	33	33	677	1	37	38	98
64	HDPXY01	PTA-868 10/26/99	pCMVSPORT 3.0	294	737	1	423		539	678	1	9	10	22
64	HDPXY01	PTA-868 10/26/99	pCMVSPORT 3.0	295	1471	105	1471		1190	679	1	16	17	25
65	HDTBV77	203070 07/27/98	pCMVSPORT 2.0	75	2181	1	2181	326	326	459	1	22	23	608
66	HDTDQ23	209965 06/11/98	pCMVSPORT 2.0	76	2207	1	2207	132	132	460	1	20	21	56

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
66	HDTDQ23	209965 06/11/98	pCMVSPORT 2.0	296	2227	1	2206	148	148	680	1	20	21	108
66	HDTDQ23	209965 06/11/98	pCMVSPORT 2.0	297	2214	1	2206	148	148	681	1	20	21	73
67	HE2DE47	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	77	3533	2821	3532	808	808	461	1	30	31	540
67	HE2DE47	97923 03/07/97 209071 05/22/97	Uni-ZAP XR	298	1145	435	1115	515	515	682	1	22	23	81
68	HE2NV57	209877 05/18/98	Uni-ZAP XR	78	867	1	867	99	99	462	1	36	37	99
69	HE2PH36	209603 01/29/98	Uni-ZAP XR	79	1558	1	1558	28	28	463	1	21	22	66
70	HE8DS15	PTA-1544 03/21/00	Uni-ZAP XR	80	2199	1	2199	91	91	464	1	24	25	72
71	HE9CO69	209551 12/12/97	Uni-ZAP XR	81	1077	1	1077	161	161	465	1	26	27	41
72	HE9HY07	209010 04/28/97 209085 05/29/97	Uni-ZAP XR	82	832	1	832	35	35	466	1	26	27	41
73	HE9OW20	203570 01/11/99	Uni-ZAP XR	83	1209	1	1209	129	129	467	1	33	34	355

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
73	HE9OW20	203570 01/11/99	Uni-ZAP XR	299	1165	1	1165	136	136	683	1	30	31	313
73	HE9OW20	203570 01/11/99	Uni-ZAP XR	300	1160	1	1160	129	129	684	1	30	31	134
74	HEEAG23	209745 04/07/98	Uni-ZAP XR	84	1669	25	1280	57	57	468	1	18	19	46
75	HEOMQ63	209563 12/18/97	pSport1	85	1336	1	1336	123	123	469	1	23	24	47
76	HEPAB80	209423 10/30/97	Uni-ZAP XR	86	799	1	799	73	73	470	1	28	29	121
76	HEPAB80	209423 10/30/97	Uni-ZAP XR	301	802	1	802	67	67	685	1	28	29	122
77	HFABG18	PTA-1544 03/21/00	Uni-ZAP XR	87	1345	1	1345	53	53	471	1	26	27	87
78	HFABH95	209407 10/23/97	Uni-ZAP XR	88	1347	1	1347	199	199	472	1	21	22	116
79	HFAEF57	209277 09/18/97	Uni-ZAP XR	89	642	1	642	232	232	473	1	42	43	86
80	HFCEB37	209008 04/28/97 209084 05/29/97	Uni-ZAP XR	90	802	352	802	487	487	474	1			10
81	HFFAD59	209242 09/12/97	Lambda ZAP II	91	470	1	470	44	44	475	1	17	18	45
82	HFGAD82	209225 08/28/97	Uni-ZAP XR	92	1881	772	1861	1019	1019	476	1	18	19	38

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
83	HFIIN69	PTA-846 10/13/99	pSport1	93	1450	1	1450	45	45	477	1	39	40	43
83	HFIIN69	PTA-846 10/13/99	pSport1	302	559	1	559	52	52	686	1	39	40	43
83	HFIIN69	PTA-846 10/13/99	pSport1	303	678	1	678		280	687	1			2
84	HFIUR10	209277 09/18/97	pSport1	94	541	1	541	50	50	478	1	22	23	44
85	HFKFG02	209627 02/12/98	Uni-ZAP XR	95	795	1	795	110	110	479	1	18	19	53
86	HFTBM50	209300 09/25/97	Uni-ZAP XR	96	762	1	740	158	158	480	1	20	21	34
87	HFTDZ36	209300 09/25/97	Uni-ZAP XR	97	1103	231	1103	547	547	481	1	22	23	68
88	HFXBL33	203071 07/27/98	Lambda ZAP II	98	1633	1	1633	152	152	482	1	24	25	162
89	HFXHK73	209580 01/14/98	Lambda ZAP II	99	1873	1	1873	247	247	483	1	36	37	67
90	HFXIX44	209782 04/20/98	Lambda ZAP II	100	1384	1	1384	98	98	484	1	18	19	47
91	HFXKY27	209877 05/18/98	Lambda ZAP II	101	945	1	945	44	44	485	1	19	20	58
92	HGBHI35	209423 10/30/97	Uni-ZAP XR	102	1437	71	1276	87	87	486	1	16	17	292
93	HGLAF75	209407 10/23/97	Uni-ZAP XR	103	776	1	776	231	231	487	1	28	29	121

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
94	HHBCS39	PTA-848 10/13/99	pCMVSPORT 1	104	2895	1	2895	104	104	488	1	26	27	166
94	HHBCS39	PTA-848 10/13/99	pCMVSPORT 1	304	1042	1	1042	150	150	688	1	26	27	166
94	HHBCS39	PTA-848 10/13/99	pCMVSPORT 1	305	1556	171	1556		1260	689	1	16	17	26
95	HHEAA08	209853 05/07/98	pCMVSPORT 3.0	105	2150	1	2150	88	88	489	1	38	39	79
95	HHEAA08	209853 05/07/98	pCMVSPORT 3.0	306	615	1	615		311	690	1	13	14	20
96	HHENV10	209368 10/16/97	pCMVSPORT 3.0	106	1155	1	1155	143	143	490	1	27	28	50
97	HHFFJ48	209627 02/12/98	Uni-ZAP XR	107	2566	1	2566	65	65	491	1	21	22	106
98	HHFHJ59	97975 04/04/97 209081 05/29/97	Uni-ZAP XR	108	661	1	661	192	192	492	1	29	30	112
99	HHGBO91	209242 09/12/97	Lambda ZAP II	109	715	1	715	140	140	493	1	28	29	49
100	HHGCG53	97899 02/26/97 209045 05/15/97	Lambda ZAP II	110	407	1	407	230	230	494	1	33	34	44

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
101	HHGCM76	97958 03/13/97 209072 05/22/97	Lambda ZAP II	111	711	8	711	270	270	495	1	22	23	89
101	HHGCM76	97958 03/13/97 209072 05/22/97	Lambda ZAP II	307	711	8	711	270	270	691	1			11
102	HHGCQ54	209300 09/25/97	Lambda ZAP II	112	875	1	875	62	62	496	1	15	16	51
103	HHPEN62	209746 04/07/98	Uni-ZAP XR	113	2152	141	2152	183	183	497	1	27	28	508
104	HJABB94	209119 06/12/97	pBluescript SK-	114	1555	1	1555	74	74	498	1	28	29	77
105	HJACG02	209215 08/21/97	pBluescript SK-	115	575	1	575	66	66	499	1	22	23	108
105	HJACG02	209215 08/21/97	pBluescript SK-	308	553	1	553	47	47	692	1	23	24	108
106	HJACG30	PTA-843 10/13/99	pBluescript SK-	116	1532	1	1532	291	291	500	1	27	28	44
106	HJACG30	PTA-843 10/13/99	pBluescript SK-	309	1614	1020	1614		50	693	1	1	2	130
106	HJACG30	PTA-843 10/13/99	pBluescript SK-	310	1087	491	1087		350	694	1	1	2	122
107	HJBCY35	209877 05/18/98	pBluescript SK-	117	1559	93	1272	232	232	501	1	23	24	327

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
108	HJPAD75	209641 02/25/98	Uni-ZAP XR	118	1231	1	1231	60	60	502	1	29	30	91
109	HKABZ65	209683 03/20/98	pCMVSPORT 2.0	119	1189	1	1189	77	77	503	1	17	18	243
109	HKABZ65	209683 03/20/98	pCMVSPORT 2.0	311	1191	1	1191	69	69	695	1	17	18	243
110	HKACD58	209346 10/09/97	pCMVSPORT 2.0	120	3153	1	3153	38	38	504	1	25	26	301
110	HKACD58	209346 10/09/97	pCMVSPORT 2.0	312	1626	1	1626	35	35	696	1	25	26	154
111	HKA EV06	209627 02/12/98	pCMVSPORT 2.0	121	2496	1	2496	501	501	505	1	30	31	438
111	HKA EV06	209627 02/12/98	pCMVSPORT 2.0	313	2351	1	2351	197	197	697	1	29	30	57
112	HKAFT66	PTA-849 10/13/99	pCMVSPORT 2.0	122	1001	270	1001	508	508	506	1	41	42	107
112	HKAFT66	PTA-849 10/13/99	pCMVSPORT 2.0	314	1001	270	1001	508	508	698	1	41	42	107
112	HKAFT66	PTA-849 10/13/99	pCMVSPORT 2.0	315	669	1	669	234	234	699	1			37
113	HKBIE57	209651 03/04/98	pCMVSPORT 1	123	1142	1038	1142	178	178	507	1	30	31	234
113	HKBIE57	209651 03/04/98	pCMVSPORT 1	316	417	1	417	30	30	700	1	26	27	46
114	HKFBC53	209782 04/20/98	ZAP Express	124	2238	1	2238	64	64	508	1	15	16	470



Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
114	HKFBC53	209782 04/20/98	ZAP Express	317	1949	1	1906	41	41	701	1	18	19	442
114	HKFBC53	209782 04/20/98	ZAP Express	318	1487	1	1487		3	702	1	1	2	309
114	HKFBC53	209782 04/20/98	ZAP Express	319	1525	1	1525		3	703	1	1	2	243
115	HKGDL36	209877 05/18/98	pSport1	125	1052	1	1052	53	53	509	1	33	34	260
115	HKGDL36	209877 05/18/98	pSport1	320	1050	1	1050	55	55	704	1	33	34	148
116	HKISB57	209603 01/29/98	pBluescript	126	1492	1	1439	130	130	510	1	19	20	95
117	HKMMW74	209463 11/14/97	pBluescript	127	1794	1	1794	202	202	511	1	21	22	41
118	HLDNA86	209277 09/18/97	pCMVSPORT 3.0	128	1346	1	1346	238	238	512	1	34	35	163
118	HLDNA86	209277 09/18/97	pCMVSPORT 3.0	321	720	1	717	45	45	705	1	31	32	92
119	HLDON23	209628 02/12/98	pCMVSPORT 3.0	129	1262	208	1256	368	368	513	1	20	21	113
120	HLDQR62	203027 06/26/98	pCMVSPORT 3.0	130	2572	427	2572	520	520	514	1	18	19	161
121	HLDQU79	203071 07/27/98	pCMVSPORT 3.0	131	1488	1	1488	99	99	515	1	23	24	348
122	HLHAL68	209746 04/07/98	Uni-ZAP XR	132	704	1	704	30	30	516	1	21	22	44

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
123	HLIBD68	203071 07/27/98	pCMVSPORT 1	133	1022	1	1022	186	186	517	1	35	36	50
124	HLICQ90	203517 12/10/98	pCMVSPORT 1	134	1766	1	1766	249	249	518	1	29	30	206
125	HLQDR48	209603 01/29/98	Lambda ZAP II	135	989	1	989	10	10	519	1	21	22	190
125	HLQDR48	209603 01/29/98	Lambda ZAP II	322	990	1	990	3	3	706	1	21	22	190
126	HLTHR66	209782 04/20/98	Uni-ZAP XR	136	2286	1	2286	5	5	520	1	34	35	75
127	HLTIP94	PTA-2076 06/09/00	Uni-ZAP XR	137	1240	1	1170	226	226	521	1	26	27	97
127	HLTIP94	PTA-2076 06/09/00	Uni-ZAP XR	323	647	1	647	226	226	707	1	26	27	65
127	HLTIP94	PTA-2076 06/09/00	Uni-ZAP XR	324	1321	870	1209		3	708	1	1	2	299
128	HLWAA17	209626 02/12/98	pCMVSPORT 3.0	138	997	246	997	436	436	522	1	15	16	187
129	HLWBK05	203331 10/08/98	pCMVSPORT 3.0	139	2383	157	2383	280	280	523	1	34	35	298
130	HLWBY76	203517 12/10/98	pCMVSPORT 3.0	140	2081	1	2081	432	432	524	1	27	28	232
131	HLWCF05	209126 06/19/97	pCMVSPORT 3.0	141	646	1	646	155	155	525	1	36	37	58
132	HLYAC95	203071 07/27/98	pSPORT1	142	312	1	312	92	92	526	1	16	17	46

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
133	HLYAN59	209346 10/09/97	pSport1	143	770	1	770	383	383	527	1	40	41	77
133	HLYAN59	209346 10/09/97	pSport1	325	729	1	729	254	254	709	1	39	40	54
134	HLYAP91	209346 10/09/97	pSport1	144	1276	1	1276	280	280	528	1	29	30	83
135	HLYES38	209853 05/07/98	pSport1	145	1223	1	1223	69	69	529	1	22	23	73
136	HMADK33	209368 10/16/97	Uni-ZAP XR	146	864	1	864	161	161	530	1	24	25	152
137	HMADS41	209563 12/18/97	Uni-ZAP XR	147	1267	1	1267	267	267	531	1	21	22	88
138	HMAMI15	PTA-2075 06/09/00	Uni-ZAP XR	148	1258	1	1258	4	4	532	1	26	27	340
138	HMAMI15	PTA-2075 06/09/00	Uni-ZAP XR	326	1084	1	1084	3	3	710	1	26	27	306
139	HMC FY13	209628 02/12/98	Uni-ZAP XR	149	883	1	883	175	175	533	1	27	28	64
140	HMDAB56	209368 10/16/97	Uni-ZAP XR	150	1465	1	1465	273	273	534	1	32	33	44
141	HMEED18	209368 10/16/97	Lambda ZAP II	151	1369	28	1369	34	34	535	1	34	35	221
142	HMEFT54	209243 09/12/97	Lambda ZAP II	152	596	1	596	332	332	536	1	19	20	39
143	HMEGF92	209243 09/12/97	Lambda ZAP II	153	629	1	611	92	92	537	1	27	28	62

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
144	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	154	2497	1	2497	531	531	538	1	26	27	64
144	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	327	1776	1	1776	528	528	711	1	26	27	64
144	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	328	784	1	784	565	565	712	1	6	7	26
144	HMSDL37	PTA-842 10/13/99	Uni-ZAP XR	329	699	275	427		2	713	1	1	2	50
145	HMSFI26	209368 10/16/97	Uni-ZAP XR	155	1217	1	1217	120	120	539	1	34	35	62
146	HMSJU68	209076 05/22/97	Uni-ZAP XR	156	1123	4	1123	272	272	540	1	31	32	49
147	HMTBI36	PTA-322 07/09/99	pCMVSPORT 3.0	157	3388	1	3388	256	256	541	1	18	19	957
147	HMTBI36	PTA-322 07/09/99	pCMVSPORT 3.0	330	3546	1	3363	255	255	714	1	18	19	957
148	HMVBS81	209628 02/12/98	pSport1	158	529	1	529	34	34	542	1	43	44	139
149	HMWDC28	209126 06/19/97	Uni-ZAP XR	159	1146	105	754	124	124	543	1	30	31	42
150	HMWFT65	209368 10/16/97	Uni-ZAP XR	160	1346	1	1346	72	72	544	1	27	28	121
151	HNEEE24	209346 10/09/97	Uni-ZAP XR	161	1079	1	1079	213	213	545	1	21	22	71
152	HNFFC43	203027 06/26/98	Uni-ZAP XR	162	2103	209	2058	488	488	546	1	12	13	68

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
153	HNFGF20	203071 07/27/98	Uni-ZAP XR	163	1370	38	1370	206	206	547	1	45	46	143
154	HNFIY77	209628 02/12/98	pBluescript	164	1212	28	1212	228	228	548	1	34	35	233
155	HNFIJ07	209463 11/14/97	Uni-ZAP XR	165	616	1	616	86	86	549	1	21	22	66
156	HNGDJ72	209299 09/25/97	Uni-ZAP XR	166	524	1	524	185	185	550	1	19	20	113
157	HNGEP09	209197 08/08/97	Uni-ZAP XR	167	1042	1	1042	72	72	551	1	15	16	82
158	HNGFR31	209407 10/23/97	Uni-ZAP XR	168	536	1	536	108	108	552	1	23	24	90
159	HNGIJ31	209236 09/04/97	Uni-ZAP XR	169	796	1	796	135	135	553	1	16	17	36
160	HNGJE50	209368 10/16/97	Uni-ZAP XR	170	1037	1	1037	77	77	554	1	36	37	46
161	HNGND37	203648 02/09/99	Uni-ZAP XR	171	841	1	841	388	388	555	1	27	28	82
162	HNGOI12	PTA-847 10/13/99	Uni-ZAP XR	172	2128	1	2128	27	27	556	1	34	35	57
162	HNGOI12	PTA-847 10/13/99	Uni-ZAP XR	331	774	1	774	27	27	715	1	34	35	57
162	HNGOI12	PTA-847 10/13/99	Uni-ZAP XR	332	1396	1	1396		596	716	1	25	26	93
163	HNHEU93	209628 02/12/98	Uni-ZAP XR	173	748	1	748	57	57	557	1	34	35	81

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
164	HNHFM14	209683 03/20/98	Uni-ZAP XR	174	297	1	297	38	38	558	1	28	29	80
165	HNHFR04	209683 03/20/98	Uni-ZAP XR	175	1681	1	1681	71	71	559	1	21	22	78
166	HNHNB29	PTA-623 09/02/99	Uni-ZAP XR	176	1894	1	1894	40	40	560	1	20	21	53
167	HNHOD46	PTA-1543 03/21/00	Uni-ZAP XR	177	1355	1	1355	12	12	561	1	20	21	80
168	HNTBI26	209563 12/18/97	pCMVSPORT 3.0	178	1382	1	1382	28	28	562	1	35	36	320
168	HNTBI26	209563 12/18/97	pCMVSPORT 3.0	333	1397	1	1397	32	32	717	1	35	36	172
168	HNTBI26	209563 12/18/97	pCMVSPORT 3.0	334	1368	1	1368	16	16	718	1	35	36	131
169	HNTBL27	209324 10/02/97	pCMVSPORT 3.0	179	791	71	791	100	100	563	1	23	24	115
170	HNTCE26	PTA-1544 03/21/00	pCMVSPORT 3.0	180	2163	830	2163	111	111	564	1	30	31	402
170	HNTCE26	PTA-1544 03/21/00	pCMVSPORT 3.0	335	1763	1	1763	57	57	719	1	28	29	121
171	HNTNC20	209782 04/20/98	pSPORT1	181	1979	1	1979	270	270	565	1	19	20	218
172	HNTNI01	209782 04/20/98	pSPORT1	182	2087	1	2087	307	307	566	1	33	34	76
172	HNTNI01	209782 04/20/98	pSPORT1	336	1274	1	1114	306	306	720	1	33	34	49

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
173	HNTSY18	PTA-855 10/18/99	pSport1	183	1811	265	1783	257	257	567	1	31	32	89
173	HNTSY18	PTA-855 10/18/99	pSport1	337	847	742	819		420	721	1	1	2	79
174	HOCNF19	203570 01/11/99	pSport1	184	1118	1	1118	166	166	568	1	20	21	87
175	HODDF13	203069 07/27/98	Uni-ZAP XR	185	830	1	830	46	46	569	1	23	24	41
176	HODDN92	209012 04/28/97 209089 06/05/97	Uni-ZAP XR	186	1939	294	1939		434	570	1	26	27	35
177	HODEJ32	203570 01/11/99	Uni-ZAP XR	187	739	1	739	358	358	571	1	21	22	43
178	HOFMQ33	PTA-848 10/13/99	pCMVSPORT 2.0	188	2410	1	2410	49	49	572	1	24	25	484
178	HOFMQ33	PTA-848 10/13/99	pCMVSPORT 2.0	338	2409	1	2409	48	48	722	1	24	25	484
178	HOFMQ33	PTA-848 10/13/99	pCMVSPORT 2.0	339	876	1	876	78	78	723	1	24	25	266
178	HOFMQ33	PTA-848 10/13/99	pCMVSPORT 2.0	340	1586	1	1586		724	724	1			5
178	HOFMQ33	PTA-848 10/13/99	pCMVSPORT 2.0	341	1011	873	1011		123	725	1	1	2	84
179	HOHBY44	PTA-867 10/26/99	pCMVSPORT 2.0	189	3369	1	3369	170	170	573	1	24	25	184

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
179	HOHBY44	PTA-867 10/26/99	pCMVSPORT 2.0	342	1063	533	1063		2	726	1	1	2	77
179	HOHBY44	PTA-867 10/26/99	pCMVSPORT 2.0	343	1178	1	1178		54	727	1	1	2	84
180	HOQBJ82	PTA-845 10/13/99	Uni-ZAP XR	190	3530	1	3530	361	361	574	1	21	22	164
180	HOQBJ82	PTA-845 10/13/99	Uni-ZAP XR	344	585	64	585	102	102	728	1	24	25	161
180	HOQBJ82	PTA-845 10/13/99	Uni-ZAP XR	345	4344	1339	1942		55	729	1	1	2	325
181	HOSBY40	209551 12/12/97	Uni-ZAP XR	191	1145	1	1145	89	89	575	1	30	31	56
182	HOSDJ25	209423 10/30/97	Uni-ZAP XR	192	2214	985	2214	1076	1076	576	1	18	19	40
182	HOSDJ25	209423 10/30/97	Uni-ZAP XR	346	1258	1	1258	146	146	730	1	18	19	40
183	HOUCQ17	209086 05/29/97	Uni-ZAP XR	193	4712	1	4693	508	508	577	1	51	52	967
184	HPEAD79	209244 09/12/97	Uni-ZAP XR	194	813	1	813	51	51	578	1	15	16	41
185	HPIBO15	209563 12/18/97	Uni-ZAP XR	195	1739	1	1739	128	128	579	1	18	19	211
185	HPIBO15	209563 12/18/97	Uni-ZAP XR	347	1739	1	1739	127	127	731	1	18	19	173
186	HPJBI33	209889 05/22/98	Uni-ZAP XR	196	1677	1	1677	236	236	580	1	31	32	53



Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
187	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	197	2648	1	2648	126	126	581	1	18	19	48
187	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	348	538	1	538	119	119	732	1	18	19	48
187	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	349	1346	1	1346		969	733	1			10
187	HPJBK12	PTA-855 10/18/99	Uni-ZAP XR	350	912	1	912	509	509	734	1			4
188	HPJCL22	PTA-2071 06/09/00	Uni-ZAP XR	198	3107	1	3107	86	86	582	1	35	36	80
188	HPJCL22	PTA-2071 06/09/00	Uni-ZAP XR	351	995	58	995	136	136	735	1	35	36	80
188	HPJCL22	PTA-2071 06/09/00	Uni-ZAP XR	352	751	183	751		232	736	1	1	2	145
189	HPMDK28	209628 02/12/98	Uni-ZAP XR	199	1084	1	1084	64	64	583	1	25	26	201
189	HPMDK28	209628 02/12/98	Uni-ZAP XR	353	1177	1	1083	58	58	737	1	25	26	201
190	HPRAL78	209195 08/01/97	Uni-ZAP XR	200	2072	1	2072	62	62	584	1	29	30	420
190	HPRAL78	209195 08/01/97	Uni-ZAP XR	354	1775	1038	1775	70	70	738	1	29	30	392
190	HPRAL78	209195 08/01/97	Uni-ZAP XR	355	866	128	866	148	148	739	1	42	43	63
191	HRABA80	209889 05/22/98	pCMVSPORT 3.0	201	1251	1	1251	144	144	585	1	27	28	102

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
191	HRABA80	209889 05/22/98	pCMVSPORT 3.0	356	1237	1	1237	130	130	740	1	27	28	102
192	HRACD15	209852 05/07/98	pCMVSPORT 3.0	202	1539	24	1539	252	252	586	1	40	41	53
192	HRACD15	209852 05/07/98	pCMVSPORT 3.0	357	1681	24	1453	252	252	741	1	40	41	53
193	HRACJ35	209878 05/18/98	pCMVSPORT 3.0	203	2077	1	2077	132	132	587	1	24	25	472
193	HRACJ35	209878 05/18/98	pCMVSPORT 3.0	358	1863	8	1863	99	99	742	1	24	25	472
193	HRACJ35	209878 05/18/98	pCMVSPORT 3.0	359	1134	1	1134		1	743	1	1	2	178
194	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	204	2108	1	2108	30	30	588	1	27	28	359
194	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	360	626	8	626	30	30	744	1	38	39	199
194	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	361	152	1	152		11	745	1			2
194	HRGBL78	PTA-841 10/13/99	Uni-ZAP XR	362	1760	127	1760		1048	746	1	10	11	32
195	HROAJ39	PTA-2069 06/09/00	Uni-ZAP XR	205	1146	224	1146	10	10	589	1	30	31	379
195	HROAJ39	PTA-2069 06/09/00	Uni-ZAP XR	363	880	1	880	31	31	747	1	15	16	283
195	HROAJ39	PTA-2069 06/09/00	Uni-ZAP XR	364	1106	224	1106	247	247	748	1	15	16	286

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
196	HROBD68	203499 12/01/98	Uni-ZAP XR	206	1998	1	1998	122	122	590	1	22	23	48
197	HSAWD74	209126 06/19/97	Uni-ZAP XR	207	970	106	970	142	142	591	1	26	27	142
197	HSAWD74	209126 06/19/97	Uni-ZAP XR	365	646	1	646	122	122	749	1	29	30	45
198	HSDEK49	209603 01/29/98	Uni-ZAP XR	208	1782	1	1782	60	60	592	1	19	20	399
198	HSDEK49	209603 01/29/98	Uni-ZAP XR	366	1590	96	1590	126	126	750	1	21	22	305
199	HSDFJ26	203648 02/09/99	Uni-ZAP XR	209	1205	23	1179	99	99	593	1	20	21	223
199	HSDFJ26	203648 02/09/99	Uni-ZAP XR	367	1179	1	1179	99	99	751	1	19	20	72
200	HSDJA15	203081 07/30/98	Uni-ZAP XR	210	1443	1	1443	247	247	594	1	20	21	152
201	HSDJM31	209148 07/17/97	Uni-ZAP XR	211	561	1	561	351	351	595	1	25	26	40
202	HSDSB09	209145 07/17/97	pBluescript	212	809	1	809	16	16	596	1	17	18	135
202	HSDSB09	209145 07/17/97	pBluescript	368	819	1	819	22	22	752	1	17	18	121
203	HSAX21	209853 05/07/98	Uni-ZAP XR	213	1986	1	1986	177	177	597	1	13	14	72
204	HSIDJ81	209551 12/12/97	Uni-ZAP XR	214	1303	1	1303	8	8	598	1	22	23	58

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
205	HSJBQ79	97924 03/07/97	Uni-ZAP XR	215	587	1	587	41	41	599	1	23	24	182
205	HSJBQ79	97924 03/07/97	Uni-ZAP XR	369	1507	164	608	57	57	753	1	19	20	327
205	HSJBQ79	97924 03/07/97	Uni-ZAP XR	370	586	4	586	35	35	754	1	23	24	184
206	HSKDA27	PTA-322 07/09/99	Uni-ZAP XR	216	4412	1	4412	786	786	600	1	24	25	950
206	HSKDA27	PTA-322 07/09/99	Uni-ZAP XR	371	1792	134	1792	127	127	755	1	21	22	509
206	HSKDA27	PTA-322 07/09/99	Uni-ZAP XR	372	1673	1	1673	12	12	756	1	21	22	554
207	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	217	1907	151	1432	353	353	601	1	23	24	260
207	HSKGN81	97977 04/04/97 209082 05/29/97	pBluescript	373	2084	335	2084	537	537	757	1	18	19	23
208	HSKNB56	209346 10/09/97	pBluescript	218	1334	449	1334	484	484	602	1	25	26	85
209	HSNAD72	209139 07/03/97	Uni-ZAP XR	219	861	1	861	220	220	603	1	19	20	35
210	HSNMC45	209300 09/25/97	Uni-ZAP XR	220	587	1	587	225	225	604	1	18	19	55

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
210	HSNMC45	209300 09/25/97	Uni-ZAP XR	374	720	1	720	232	232	758	1	17	18	25
211	HSQFP66	209126 06/19/97	Uni-ZAP XR	221	477	1	477	96	96	605	1	32	33	78
212	HSRFZ57	PTA-622 09/02/99	Uni-ZAP XR	222	1930	1	1925	82	82	606	1	18	19	41
213	HSUBW09	209007 04/28/97 209083 05/29/97	Uni-ZAP XR	223	1021	1	1021	153	153	607	1	31	32	56
214	HSVBU91	209603 01/29/98	Uni-ZAP XR	224	727	1	727	256	256	608	1	18	19	90
215	HSXGI47	PTA-499 08/11/99	Uni-ZAP XR	225	1256	1	1256	87	87	609	1	21	22	57
216	HSYAZ63	PTA-163 06/01/99	pCMVSPORT 3.0	226	3466	1655	3347	448	448	610	1	30	31	434
216	HSYAZ63	PTA-163 06/01/99	pCMVSPORT 3.0	375	1707	1	1707	215	215	759	1	21	22	40
217	HSYBG37	209463 11/14/97	pCMVSPORT 3.0	227	1238	1	1238	47	47	611	1	24	25	305
217	HSYBG37	209463 11/14/97	pCMVSPORT 3.0	376	1239	1	1239	48	48	760	1	24	25	305
218	HTADW91	PTA-1543 03/21/00	Uni-ZAP XR	228	1481	54	1481	59	59	612	1	32	33	364
219	HTAEE28	PTA-843 10/13/99	Uni-ZAP XR	229	1341	1	1341	319	319	613	1	33	34	282

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
219	HTAEE28	PTA-843 10/13/99	Uni-ZAP XR	377	738	159	738	372	372	761	1	33	34	122
219	HTAEE28	PTA-843 10/13/99	Uni-ZAP XR	378	935	1	807		124	762	1	1	2	216
220	HTDAF28	97974 04/04/97 209080 05/29/97	pSport1	230	912	1	912	38	38	614	1	22	23	87
221	HTECC05	209877 05/18/98	Uni-ZAP XR	231	839	1	839	13	13	615	1	15	16	178
221	HTECC05	209877 05/18/98	Uni-ZAP XR	379	871	1	871	21	21	763	1	15	16	127
221	HTECC05	209877 05/18/98	Uni-ZAP XR	380	881	1	881	27	27	764	1	15	16	164
222	HTEEB42	97922 03/07/97 209070 05/22/97	Uni-ZAP XR	232	1022	20	1022	59	59	616	1	22	23	298
223	HTEFU65	209324 10/02/97	Uni-ZAP XR	233	1028	1	1028	231	231	617	1	24	25	46
224	HTEGA76	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	234	450	1	450	90	90	618	1	43	44	65

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
225	HTEJN13	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	235	1094	1	1094	156	156	619	1	15	16	208
225	HTEJN13	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	381	1147	1	1147	163	163	765	1	15	16	159
225	HTEJN13	97958 03/13/97 209072 05/22/97	Uni-ZAP XR	382	1134	1	1134	155	155	766	1	19	20	71
226	HTELP17	203648 02/09/99	Uni-ZAP XR	236	808	1	808	164	164	620	1	20	21	44
227	HTELS08	PTA-1544 03/21/00	Uni-ZAP XR	237	1898	1	1898	15	15	621	1	17	18	158
228	HTLEP53	209641 02/25/98	Uni-ZAP XR	238	818	1	818	73	73	622	1	43	44	101
229	HTOIY21	209852 05/07/98	Uni-ZAP XR	239	1558	1	1558	91	91	623	1	14	15	231
230	HTPCS72	209423 10/30/97	Uni-ZAP XR	240	3435	2141	3431	2365	2365	624	1	29	30	71
230	HTPCS72	209423 10/30/97	Uni-ZAP XR	383	1598	306	1598	530	530	767	1	29	30	71
231	HTPIH83	PTA-871 10/26/99	Uni-ZAP XR	241	1481	1	1481	118	118	625	1	24	25	230

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
231	HTPIH83	PTA-871 10/26/99	Uni-ZAP XR	384	530	1	530	111	111	768	1	24	25	140
231	HTPIH83	PTA-871 10/26/99	Uni-ZAP XR	385	1046	359	1046		96	769	1	1	2	86
232	HTSEW17	209138 07/03/97	pBluescript	242	652	1	652	170	170	626	1	34	35	37
233	HTTB176	209641 02/25/98	Uni-ZAP XR	243	1711	1	1711	133	133	627	1	22	23	133
234	HTTBS64	PTA-841 10/13/99	Uni-ZAP XR	244	2058	1	2058	95	95	628	1	17	18	42
234	HTTBS64	PTA-841 10/13/99	Uni-ZAP XR	386	819	1	819	100	100	770	1	17	18	42
234	HTTBS64	PTA-841 10/13/99	Uni-ZAP XR	387	501	1	501		175	771	1	1	2	76
235	HTWKE60	209651 03/04/98	Lambda ZAP II	245	407	1	407	185	185	629	1	25	26	44
236	HTXAJ12	209423 10/30/97	Uni-ZAP XR	246	675	1	675	91	91	630	1	18	19	111
236	HTXAJ12	209423 10/30/97	Uni-ZAP XR	388	675	1	675	91	91	772	1	18	19	111
237	HTXJM03	209580 01/14/98	Uni-ZAP XR	247	2398	211	2398	328	328	631	1	18	19	56
238	HTXKF95	PTA-622 09/02/99	Uni-ZAP XR	248	975	170	966	421	421	632	1	28	29	78
238	HTXKF95	PTA-622 09/02/99	Uni-ZAP XR	389	884	79	875	330	330	773	1	28	29	78



Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
239	HTXON32	203648 02/09/99	Uni-ZAP XR	249	1505	1	1505	72	72	633	1	22	23	52
240	HUFCJ30	209641 02/25/98	pSport1	250	868	1	868	123	123	634	1	29	30	50
241	HUVEB53	209603 01/29/98	Uni-ZAP XR	251	1502	1	1502	14	14	635	1	20	21	45
242	HWAAD63	203570 01/11/99	pCMVSPORT 3.0	252	3308	1	3308	322	322	636	1	30	31	168
242	HWAAD63	203570 01/11/99	pCMVSPORT 3.0	390	3306	1	3306	322	322	774	1	30	31	53
242	HWAAD63	203570 01/11/99	pCMVSPORT 3.0	391	2194	1	2194	312	312	775	1	30	31	169
243	HWADJ89	PTA-1543 03/21/00	pCMVSPORT 3.0	253	1769	529	1769	581	581	637	1	1	2	43
244	HWBCP79	209641 02/25/98	pCMVSPORT 3.0	254	1138	1	1138	243	243	638	1	21	22	105
244	HWBCP79	209641 02/25/98	pCMVSPORT 3.0	392	1138	1	1138	233	233	776	1	21	22	105
245	HWBEM18	PTA-868 10/26/99	pCMVSPORT 3.0	255	6729	1	6729	75	75	639	1	25	26	1887
245	HWBEM18	PTA-868 10/26/99	pCMVSPORT 3.0	393	3599	1	3599	65	65	777	1	25	26	886
245	HWBEM18	PTA-868 10/26/99	pCMVSPORT 3.0	394	2924	1	2496		1	778	1	1	2	498
246	HWBFX31	PTA-1543 03/21/00	pCMVSPORT 3.0	256	1677	1	1677	271	271	640	1	1	2	52

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
247	HWHGZ51	PTA-499 08/11/99	pCMVSPORT 3.0	257	1699	1	1699	33	33	641	1	30	31	346
248	HWTBK81	209138 07/03/97	Uni-ZAP XR	258	637	78	635	139	139	642	1	23	24	155
249	HAGAI85	97922 03/07/97 209070 05/22/97	Uni-ZAP XR	259	1752	52	1752	166	166	653	1	23	24	30
250	HOFOC33	PTA-848 10/13/99	pCMVSPORT 2.0	260	1669	1	1669	76	76	654	1	21	22	363
251	HSDEZ20	209852 05/07/98	Uni-ZAP XR	261	795	1	795	58	58	655	1	41	42	122

### **Table 1B (Comprised of Tables 1B.1 and 1B.2)**

The first column in Table 1B.1 and Table 1B.2 provides the gene number in the application corresponding to the clone identifier. The second column in Table 1B.1 and Table 1B.2 provides a unique "Clone ID:" for the cDNA clone related to each contig sequence disclosed in Table 1B.1 and Table 1B.2. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X as determined by directly sequencing the referenced clone. The referenced clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein. The third column in Table 1B.1 and Table 1B.2 provides a unique "Contig ID" identification for each contig sequence. The fourth column in Table 1B.1 and Table 1B.2 provides the "SEQ ID NO:" identifier for each of the contig polynucleotide sequences disclosed in Table 1B.

#### **Table 1B.1**

The fifth column in Table 1B.1, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1B.1, column 6, as SEQ ID NO:Y. Where the nucleotide position number "To" is lower than the nucleotide position number "From", the preferred ORF is the reverse complement of the referenced polynucleotide sequence. The sixth column in Table 1B.1 provides the corresponding SEQ ID NO:Y for the polypeptide sequence encoded by the preferred ORF delineated in column 5. In one embodiment, the invention provides an amino acid sequence comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by "ORF (From-To)". Also provided are polynucleotides encoding such amino acid sequences and the complementary strand thereto. Column 7 in Table 1B.1 lists residues comprising epitopes contained in the polypeptides encoded by the preferred ORF (SEQ ID NO:Y), as predicted using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, at least one, two, three, four, five or more of the predicted epitopes as described in Table 1B. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly.

Column 8 in Table 1B.1 provides a chromosomal map location for certain polynucleotides of the invention. Chromosomal location was determined by finding exact matches to

EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Each sequence in the UniGene database is assigned to a "cluster"; all of the ESTs, cDNAs, and STSs in a cluster are believed to be derived from a single gene. Chromosomal mapping data is often available for one or more sequence(s) in a UniGene cluster; this data (if consistent) is then applied to the cluster as a whole. Thus, it is possible to infer the chromosomal location of a new polynucleotide sequence by determining its identity with a mapped UniGene cluster.

A modified version of the computer program BLASTN (Altshul, et al., J. Mol. Biol. 215:403-410 (1990), and Gish, and States, Nat. Genet. 3:266-272) (1993) was used to search the UniGene database for EST or cDNA sequences that contain exact or near-exact matches to a polynucleotide sequence of the invention (the 'Query'). A sequence from the UniGene database (the 'Subject') was said to be an exact match if it contained a segment of 50 nucleotides in length such that 48 of those nucleotides were in the same order as found in the Query sequence. If all of the matches that met this criteria were in the same UniGene cluster, and mapping data was available for this cluster, it is indicated in Table 1B under the heading "Cytologic Band". Where a cluster had been further localized to a distinct cytologic band, that band is disclosed; where no banding information was available, but the gene had been localized to a single chromosome, the chromosome is disclosed.

Once a presumptive chromosomal location was determined for a polynucleotide of the invention, an associated disease locus was identified by comparison with a database of diseases which have been experimentally associated with genetic loci. The database used was the Morbid Map, derived from OMIM™ and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000;. If the putative chromosomal location of a polynucleotide of the invention (Query sequence) was associated with a disease in the Morbid Map database, an OMIM reference identification number was noted in column 9, Table 1B.1, labelled "OMIM Disease Reference(s). Table 5 is a key to the OMIM reference identification numbers (column 1), and provides a description of the associated disease in Column 2.

#### **Table 1B.2**

Column 5, in Table 1B.2, provides an expression profile and library code:count for each of the contig sequences (SEQ ID NO:X) disclosed in Table 1B, which can routinely be combined with the information provided in Table 4 and used to determine the tissues, cells, and/or cell line libraries which predominantly express the polynucleotides of the invention. The first number in Table 1B.2, column 5 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. The second number in column 5 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence was identified in the corresponding tissue/cell source. Those tissue/cell source identifier codes in

which the first two letters are “AR” designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of <sup>33</sup>P dCTP, using oligo (dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after “[array code]:” represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

Table 1B.1

Gene No:	cDNA Clone ID	Contig ID:	SEQ ID NO: X	ORF (From-To)	AA SEQ ID NO: Y	Predicted Epitopes	Tissue Distribution Library code: count (see Table IV for Library Codes)	Cytologic Band	OMIM Disease Reference(s):
1	H2CBU83	884134	11	157 - 777	405	Pro-62 to Asp-67, Arg-74 to Gly-80, Gln-146 to Glu-168.	S0414: 9, S0422: 7, L0662: 7, S0444: 6, L0748: 4, L0581: 4, S0442: 3, H0031: 3, L0666: 3, L0754: 3, H0656: 2, S0358: 2, S0360: 2, H0013: 2, S0438: 2, S0440: 2, L0598: 2, L0803: 2, L0540: 2, L0756: 2, L0752: 2, L0758: 2, L0759: 2, S0242: 2, H0624: 1, S0282: 1, H0742: 1, H0393: 1, H0586: 1, H0574: 1, H0036: 1, H0004: 1, T0103: 1, T0110: 1, H0571: 1, H0569: 1, H0123: 1, L0471: 1, H0594: 1, S6028: 1, H0622: 1, UNKWN: 1, L0649: 1, L0381: 1, L0776: 1, L0659: 1, L0528: 1, L0792: 1, L0793: 1, L0663: 1, L0664: 1, L0665: 1, L2257: 1, H0144: 1, S0374: 1, H0547: 1,		

									H0593: 1, H0690: 1, H0670: 1, H0648: 1, H0672: 1, H0651: 1, H0539: 1, S0378: 1, S0380: 1, H0521: 1, S0406: 1, H0555: 1, H0478: 1, L0744: 1, L0731: 1 and S0276: 1.			
	H2CBU83	745366	262	157 - 312	656							
2	H6EDC19	543259	12	389 - 733	406	Arg-5 to Pro-12.			L0805: 4, H0559: 3, L0803: 3, H0545: 2, L0664: 2, L0748: 2, L0777: 2, L0758: 2, L3643: 1, H0295: 1, H0657: 1, S0444: 1, H0734: 1, H0550: 1, S0222: 1, T0048: 1, H0318: 1, H0052: 1, H0231: 1, H0041: 1, H0620: 1, H0606: 1, H0316: 1, H0077: 1, L0769: 1, L0761: 1, L0766: 1, L0774: 1, L0789: 1, H0672: 1, H0539: 1, S0146: 1, L0751: 1, L0780: 1, L0731: 1, S0434: 1 and S0196: 1.			
3	HACBD91	637482	13	117 - 266	407				L0748: 8, L0439: 4, L0749: 3, H0171: 2, L3659: 2, L0438: 2, S6024: 1, S0360: 1, H0640: 1, S0278: 1,			





									H0375: 1, S6028: 1, H0687: 1, H0424: 1, H0708: 1, H0163: 1, H0063: 1, H0743: 1, L5565: 1, L0800: 1, L0783: 1, L5622: 1, L0665: 1, S0216: 1, H0693: 1, L0438: 1, H0520: 1, H0593: 1, S0378: 1, S0044: 1, H0555: 1, S0037: 1, L0742: 1, L0748: 1, L0749: 1, L0750: 1, L0758: 1, L0759: 1, S0260: 1 and L0599: 1.				
5	HACCI17 HAGAQ26	731877 561996	263 15	135 - 353 251 - 439	657 409				L0603: 4, H0031: 3, S0010: 2, T0010: 2, H0644: 2, L0438: 2, H0038: 1, H0616: 1, H0264: 1, S0426: 1, H0539: 1, L0439: 1 and S0260: 1.				
6	HAGDS35	1352199	16	45 - 410	410	Leu-31 to Phe-38, Glu-47 to Trp-52.			L0748: 8, L0777: 5, H0013: 3, S0356: 2, H0622: 2, L0794: 2, L0803: 2, L0665: 2, L0438: 2, H0436: 2, L0743: 2, L0740: 2, H0170: 1, S0354: 1, S0376: 1, H0749: 1, H0586: 1, S0010: 1, S6028: 1, H0188: 1,				

								H0616: 1, S0422: 1, L0764: 1, L0521: 1, L0804: 1, L0774: 1, L0776: 1, L0655: 1, L0659: 1, L5623: 1, H0520: 1, H0435: 1, L0439: 1, L0754: 1, L0747: 1, L0779: 1, L0758: 1, L0759: 1, S0026: 1, H0543: 1 and H0423: 1.			
	HAGDS35	543617	264	52 - 405	658	Leu-31 to Phe-38, Glu-47 to Trp-52.					
7	HAGFI62	70425	17	429 - 704	411	Gly-49 to Ser-54, Lys-61 to Arg-68.		L0439: 5, S0051: 3, S0007: 2, S0422: 2, L0438: 2, H0171: 1, S0360: 1, H0411: 1, H0431: 1, S0010: 1, H0569: 1, S0388: 1, H0163: 1, H0100: 1, L0805: 1, L0809: 1, S0126: 1, S0406: 1, L0742: 1, L0744: 1, L0747: 1, L0779: 1 and L0758: 1.			
8	HAHDB16	635412	18	93 - 245	412	/		H0599: 1			
9	HAICP19	422672	19	128 - 1468	413	Asn-27 to Leu-47, Gln-81 to Lys-88, Asp-93 to Lys-102, Asn-107 to Leu-116, Met-129 to Glu-141, Glu-150 to Asp-157, Lys-176 to Glu-185,		H0618: 3, L0755: 3, S0436: 3, S0356: 2, H0253: 2, H0309: 2, H0123: 2, H0553: 2, L0369: 2, L0771: 2, L0774: 2, L0806: 2, L0807: 2, L0666: 2,			





13	HAMFE15	905695	23	1495 - 2757	417	<p>Leu-8 to Thr-16,  Gly-93 to Ala-105,  Arg-136 to Thr-142,  Lys-195 to Gln-200,  Lys-241 to His-247,  Gly-255 to Gln-270,  Gln-288 to Leu-293,  Thr-316 to Asp-328,  Gly-348 to Pro-355,  Asp-408 to Met-415.</p>	<p>H0435: 1, H0518: 1,  H0521: 1, H0626: 1,  L0748: 1, S0436: 1,  L0591: 1, H0542: 1,  S0424: 1 and H0677: 1.  L0748: 10, L0754: 9,  L0731: 9, L0766: 8,  L0439: 7, L0803: 6,  H0624: 5, L0759: 5,  S0356: 4, H0486: 4,  H0090: 4, L0789: 4,  L0438: 4, L0740: 4,  L0749: 4, L0756: 4,  L0777: 4, L0599: 4,  S0360: 3, H0013: 3,  S0003: 3, L0369: 3,  L0794: 3, L0659: 3,  L0809: 3, L0665: 3,  H0539: 3, L0362: 3,  S0114: 2, S0358: 2,  S0278: 2, H0441: 2,  H0586: 2, H0333: 2,  H0581: 2, H0328: 2,  H0553: 2, H0529: 2,  L0770: 2, L0662: 2,  L0804: 2, L0666: 2,  L0663: 2, H0547: 2,  H0519: 2, H0659: 2,  H0670: 2, S0330: 2,  L0747: 2, L0750: 2,  L0755: 2, L0758: 2,  L0589: 2, L0592: 2,  L0581: 2, L0593: 2,</p>		
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									L0780: 2, S0420: 1, S0442: 1, S0444: 1, S0045: 1, L3316: 1, H0599: 1, H0575: 1, S0474: 1, T0115: 1, H0083: 1, H0510: 1, H0644: 1, H0551: 1, S0386: 1, H0494: 1, H0561: 1, H0538: 1, S0422: 1, L0646: 1, L0804: 1, L0774: 1, L0809: 1, L0530: 1, L0663: 1, L0664: 1, L0665: 1, H0593: 1, S0380: 1, S0027: 1, L0748: 1, L0439: 1, L0756: 1, L0755: 1, L0758: 1, L0485: 1, H0542: 1 and H0423: 1.			
	HAPOM49	722386	268	448 - 816	662	Met-1 to Cys-21, Cys-41 to Asp-59, Pro-104 to His-116.						
18	HAPUC89	834358	28	385 - 807	422		H0575: 1					
19	HATBR65	635514	29	252 - 446	423	Ile-25 to Trp-30.	L0534: 4, L0562: 3, L0527: 3, H0254: 2, S0045: 2, H0156: 2, L0589: 2, H0255: 1, H0402: 1, L0539: 1, T0060: 1, H0328: 1, H0615: 1, H0598: 1, H0264: 1, L0766: 1, L0493: 1, L0666: 1, S0052: 1, H0539: 1,					

									L0747: 1, L0752: 1 and L0366: 1.			
20	HAUAI83	639009	30	253 - 399	424		Asn-34 to Lys-42.		H0294: 2	19		
	HAUAI83	383592	269	575 - 643	663		Ala-17 to Lys-23.					
21	HBAMB15	671835	31	390 - 569	425				H0410: 1, H0530: 1, H0328: 1, L0455: 1 and L0740: 1.			
22	HBGBA69	1352289	32	124 - 843	426		Pro-51 to Asp-56, Gly-95 to Thr-105, Val-132 to Ala-138, Pro-229 to Leu-240.		S0474: 13, L0747: 7, S0410: 6, H0617: 5, L0777: 5, H0618: 4, H0521: 4, H0661: 3, H0663: 3, S0360: 3, H0052: 3, H0545: 3, H0038: 3, L0766: 3, S0380: 3, L0740: 3, L0751: 3, L0757: 3, H0653: 3, S0358: 2, H0733: 2, L0717: 2, S0278: 2, H0318: 2, H0309: 2, H0327: 2, H0150: 2, H0687: 2, H0181: 2, H0413: 2, H0509: 2, L0769: 2, L0764: 2, L0771: 2, L0662: 2, L0768: 2, L0774: 2, L0776: 2, L5622: 2, L0666: 2, L0663: 2, L2261: 2, S0126: 2, H0658: 2, S0406: 2, L0744: 2, L0758: 2, L0588: 2, L3643: 1, S0342: 1, H0713: 1, H0740: 1,			



									S0044: 1, H0555: 1, H0436: 1, S3014: 1, L0439: 1, L0749: 1, L0731: 1, L0759: 1, S0260: 1, H0445: 1, S0434: 1, S0196: 1, H0423: 1 and H0506: 1.			
	HBGBA69	709658	270	62 - 244	664	Thr-52 to Gly-57.						
23	HBGNU56	1352412	33	125 - 679	427	Thr-19 to Ala-33, Leu-54 to Asp-82, Pro-89 to Ala-97, Pro-100 to Lys-125, Ser-127 to Phe-135, Ser-180 to Ser-185.			H0617: 7, S0114: 5, H0486: 5, H0069: 5, S0344: 5, L0794: 5, H0436: 5, L0748: 5, H0341: 4, H0255: 4, L0744: 4, S0436: 4, H0295: 3, H0294: 3, T0049: 3, H0661: 3, S0356: 3, S0476: 3, H0581: 3, H0271: 3, H0038: 3, H0087: 3, H0529: 3, L0364: 3, L0766: 3, S0126: 3, L0747: 3, L0749: 3, H0423: 3, H0740: 2, H0657: 2, S0376: 2, H0497: 2, H0635: 2, H0616: 2, S0440: 2, S0144: 2, S0142: 2, L0771: 2, L0378: 2, L0806: 2, L0518: 2, H0658: 2, S0044: 2, S3014: 2, S0027: 2, L0754: 2, L0777: 2, L0731: 2, H0445: 2,			





									L0381: 1, L0775: 1, L0805: 1, L0654: 1, L0776: 1, L0655: 1, L0657: 1, L0656: 1, L0382: 1, L0809: 1, L0543: 1, L0791: 1, L0666: 1, L0664: 1, H0697: 1, H0699: 1, H0689: 1, H0690: 1, H0660: 1, H0518: 1, H0521: 1, H0696: 1, S0406: 1, H0576: 1, S3012: 1, L0743: 1, L0780: 1, L0757: 1, L0759: 1, S0031: 1, L0593: 1, L0595: 1, H0542: 1, H0543: 1, H0422: 1 and H0506: 1.			
	HBGNU56	1094642	271	79 - 612	665	Thr-19 to Ala-33, Leu-54 to Asp-82, Pro-89 to Ala-97, Pro-100 to Lys-125, Ser-127 to Phe-135, Gly-164 to Leu-169, Cys-173 to Arg-178.						
	HBGNU56	1050255	272	2 - 658	666	Arg-16 to Ser-31.						
24	HBIAE26	514418	34	75 - 194	428	Ser-22 to Lys-27.			S0049: 1 and S0146: 1.			
25	HBINS58	1352386	35	57 - 578	429	Gly-32 to Gly-37, Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122, Lys-164 to Tyr-170.		1	H0593: 2, H0617: 1, L0657: 1 and L0592: 1.			
	HBINS58	961712	273	71 - 592	667	Gly-32 to Gly-37,						

							Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122, Lys-164 to Gln-171.				
	HBINS58	892924	274	100 - 732	668		Gly-32 to Gly-37, Glu-78 to His-87, Tyr-102 to Ala-107, Pro-115 to Val-122.				
26	HBJFU48	460392	36	20 - 142	430				H0255: 2, H0318: 2, H0341: 1, L0519: 1, S0053: 1 and L0748: 1.		
27	HBJLC01	638410	37	87 - 227	431				H0318: 1		
28	HBNAW17	526797	38	77 - 262	432				L0766: 3 and H0188: 1.		
29	HCE2F54	634016	39	166 - 1125	433		His-44 to Pro-50, Glu-90 to Glu-96, Gln-111 to Glu-117, Ser-143 to Gly-151, Ala-154 to Leu-166, Pro-199 to Ala-216, Gly-264 to Asp-272.		H0052: 9, L0794: 6, L0758: 6, L0659: 5, L0666: 4, L0438: 4, S0126: 4, L0754: 4, L0779: 4, H0617: 3, L0748: 3, L0751: 3, L0759: 3, H0333: 2, H0013: 2, H0150: 2, H0494: 2, L0761: 2, L0641: 2, L0649: 2, L0809: 2, L0519: 2, L0663: 2, S0380: 2, L3832: 2, L0439: 2, L0747: 2, L0749: 2, H0685: 1, H0713: 1, H0295: 1, H0341: 1, H0484: 1, H0255: 1, H0638: 1, S0358: 1, S0046: 1, S0476: 1, H0393: 1, L3388: 1,		





									L0666: 1, L0664: 1, L0665: 1, S0053: 1, L0710: 1, L2654: 1, H0547: 1, H0682: 1, H0435: 1, H0670: 1, H0660: 1, H0648: 1, H0672: 1, S0328: 1, H0539: 1, S0152: 1, H0696: 1, S0044: 1, S0406: 1, H0631: 1, S3014: 1, S0028: 1, L0742: 1, L0749: 1, L0753: 1, L0759: 1, S0436: 1, S0011: 1, S0192: 1, H0542: 1, H0423: 1, S0398: 1 and H0506: 1.				
	HCE3G69	494346	275	165 - 482	669	Lys-50 to Leu-69.			L0777: 10, L0756: 4, S0414: 3, L0659: 3, L0740: 3, H0441: 2, S0003: 2, H0616: 2, L0766: 2, H0144: 2, L0439: 2, L0780: 2, L0759: 2, L0596: 2, S0242: 2, H0542: 2, S0470: 1, S0342: 1, H0341: 1, S0001: 1, S0282: 1, S0408: 1, S0007: 1, T0060: 1, H0427: 1, H0098: 1, H0042: 1, H0581: 1, S0049: 1, H0052: 1,				
31	HCE5F43	612796	41	113 - 931	435	Asn-23 to Ser-32, Trp-61 to Ser-68, Ala-130 to Ala-135, Thr-141 to Gly-148, Asn-176 to Gly-182, Pro-197 to Glu-205, His-211 to Glu-222, Gln-242 to Ile-248, Thr-265 to Leu-271.							

									H0024: 1, H0051: 1, H0647: 1, S0422: 1, L0770: 1, L0769: 1, L0772: 1, L0662: 1, L0794: 1, L0803: 1, L0805: 1, L0666: 1, L0663: 1, L0664: 1, S0374: 1, S0126: 1, H0648: 1, H0696: 1, L0747: 1, L0752: 1, L0755: 1 and L0591: 1.			
32	HCEFB80	1143407	42	12 - 281	436	Met-1 to Ala-8, Ser-51 to Leu-62, Pro-70 to Lys-78.			H0052: 6, L0439: 5, L0794: 3, L0748: 3, L0415: 2, H0661: 2, H0559: 2, S0049: 2, H0327: 2, S0051: 2, H0399: 2, S0036: 2, L0351: 2, L0770: 2, H0144: 2, L0758: 2, L0759: 2, S0116: 1, S0110: 1, H0637: 1, H0261: 1, S0222: 1, H0438: 1, H0013: 1, H0569: 1, H0320: 1, S0422: 1, H0529: 1, L0638: 1, L0517: 1, L0438: 1, S0126: 1, L0749: 1, L0756: 1 and L0592: 1.	22		
	HCEFB80	1046853	276	5 - 274	670	Met-1 to Ala-8.						
33	HCENK38	658737	43	10 - 168	437	Tyr-30 to Ser-40.			L0747: 15, L0745: 12, L0746: 12, L0754: 9, L0439: 6, S0007: 5,			



									H0131: 1, H0633: 1, L0769: 1, L0638: 1, L0667: 1, L0764: 1, L0771: 1, L0521: 1, L0649: 1, L0774: 1, L0775: 1, L0523: 1, L0776: 1, L0655: 1, L0527: 1, L0636: 1, L0519: 1, S0053: 1, L0438: 1, L0352: 1, H0520: 1, H0689: 1, H0690: 1, H0658: 1, H0660: 1, H0648: 1, H0710: 1, S0350: 1, S0044: 1, S0146: 1, H0436: 1, L0611: 1, L0749: 1, L0786: 1, S0436: 1, L0362: 1, L0366: 1, S0026: 1, H0667: 1, H0542: 1 and H0422: 1.				
34	HCEWE20	543370	44	166 - 321	438	Ser-17 to Gln-22.			H0052: 2, H0261: 1, H0271: 1 and S0458: 1.				
35	HCFOM18	553582	45	28 - 219	439				H0423: 1				
36	HCGMD59	636078	46	438 - 662	440				L0748: 6, L0750: 4, S0386: 3, L0439: 3, L0777: 3, H0624: 2, H0052: 2, L0435: 2, L0598: 2, L0809: 2, L0751: 2, L0747: 2, L0756: 2, L0753: 2, L0731: 2, H0422: 2, L0718: 2, H0265: 1,				



									H0381: 1, H0459: 1, S0356: 1, S0360: 1, H0619: 1, H0393: 1, H0411: 1, H0050: 1, L0455: 1, H0412: 1, S0344: 1, L0769: 1, L0638: 1, L0764: 1, L0771: 1, L0803: 1, L0804: 1, L0805: 1, L0776: 1, L0438: 1, H0689: 1, H0659: 1, H0658: 1, H0660: 1, H0666: 1, L0594: 1 and S0106: 1.			
37	HCNDR47	1016919	47	21 - 401	441	Pro-71 to His-92.		L0794: 3, L0764: 2, L0439: 2, H0052: 1, H0597: 1, T0006: 1, L0766: 1, H0648: 1, S0330: 1 and L0753: 1.	1			
	HCNDR47	863677	277	124 - 507	671	Pro-71 to His-92.						
	HCNDR47	874128	278	603 - 632	672	Leu-1 to Thr-9.						
38	HCNSB61	526413	48	218 - 349	442	Pro-26 to Asn-32.		H0231: 1 and S0216: 1.				
39	HCQCT05	911924	49	381 - 389	443			S0356: 4, H0596: 2, H0032: 2, H0685: 1, S0442: 1, H0270: 1, H0156: 1, H0046: 1, H0622: 1, L0483: 1, H0674: 1, S0440: 1, L0372: 1, L0364: 1, L0805: 1, L0663: 1, S0374: 1, S0434: 1 and L0599: 1.				
	HCQCT05	906285	279	1702 - 1710	673							

40	HCUGM86	847040	50	91 - 225	444		H0402: 1, H0779: 1 and L0747: 1.		
41	HCUIM65	550208	51	557 - 700	445		L0789: 4, L0809: 2, L0759: 2, L0596: 2, H0306: 1, H0402: 1, H0580: 1, H0550: 1, H0370: 1, H0404: 1, H0559: 1, H0486: 1, H0031: 1, H0674: 1, H0135: 1, H0100: 1, L0800: 1, L0794: 1, L0804: 1, L0805: 1, L0515: 1, L0783: 1, H0672: 1, L0777: 1, H0444: 1 and H0352: 1.	19p13.3	108725, 109480, 111250, 120700, 130130, 130130, 133171, 136836, 145981, 147141, 147840, 164953, 181800, 188070, 277600, 600957, 601238, 601240, 601768, 601846, 602018, 602216, 602216, 602216, 602477, 605248
42	HCWDS72	707833	52	19 - 318	446		L0752: 30, L0754: 17, L0740: 16, H0521: 14, L0439: 14, L0766: 12, S0003: 11, S0214: 11, L0777: 10, S0002: 8,		



					L0807: 2, L0659: 2, L0664: 2, L0438: 2, H0648: 2, H0672: 2, S0406: 2, S0028: 2, L0588: 2, L0599: 2, H0667: 2, S0196: 2, H0624: 1, H0171: 1, H0265: 1, S0040: 1, H0713: 1, S0114: 1, L0811: 1, H0341: 1, S0212: 1, S0001: 1, H0661: 1, H0305: 1, S0418: 1, L3649: 1, H0741: 1, S0045: 1, H0747: 1, S0132: 1, S0476: 1, L3089: 1, H0619: 1, H0415: 1, H0409: 1, L1942: 1, L2495: 1, L3655: 1, H0013: 1, S0010: 1, S0665: 1, H0327: 1, H0046: 1, L0157: 1, S0051: 1, T0010: 1, H0266: 1, H0179: 1, H0615: 1, H0096: 1, H0031: 1, H0553: 1, L0055: 1, H0674: 1, H0163: 1, H0038: 1, H0264: 1, H0413: 1, L0564: 1, H0560: 1, H0359: 1, H0509: 1, S0142: 1, S0344: 1, UNKWN: 1, L0369: 1,				
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									L0762: 1, L0371: 1, L0796: 1, L0761: 1, L0373: 1, L0773: 1, L0521: 1, L0794: 1, L0804: 1, L0784: 1, L0518: 1, L0783: 1, L0647: 1, L5622: 1, L5623: 1, L3391: 1, L2657: 1, L2262: 1, L3636: 1, H0144: 1, H0684: 1, H0659: 1, H0658: 1, S0330: 1, S0152: 1, H0696: 1, S0404: 1, S0037: 1, L0746: 1, L0779: 1, S0031: 1, H0707: 1, S0434: 1, L0480: 1, L0608: 1, L0604: 1, S0011: 1, S0192: 1, S0456: 1 and H0506: 1.				
43	HCWKC15	553621	53	37 - 159	447	Lys-28 to Thr-34.	H0305: 2 and H0589: 1.						
44	HCWUM50	639037	54	270 - 407	448		L0766: 8, H0265: 4, H0556: 4, L0748: 2, S0114: 1, H0589: 1, H0587: 1, H0052: 1, H0264: 1, T0041: 1, H0539: 1 and H0187: 1.						
45	HDABR72	1301517	55	33 - 473	449	Leu-30 to Gly-38, Arg-67 to Val-72, Val-76 to Ala-89, Pro-118 to Arg-123, Gly-129 to Ala-136, Leu-138 to Arg-146.	S0410: 1, H0497: 1, H0013: 1, H0635: 1, H0040: 1, L0766: 1, H0436: 1, S3014: 1 and S0027: 1.						

	HDABR72	748225	280	28 - 468	674	Leu-30 to Gly-38, Arg-67 to Val-72, Val-76 to Ala-89, Pro-118 to Arg-123, Gly-129 to Ala-136, Leu-138 to Arg-146.			
46	HDPBA28	1062783	56	259 - 3084	450	Gln-33 to Trp-49, Gly-161 to Gly-172, Ile-207 to Arg-212, Asn-414 to Val-419, Val-423 to Gln-428, Val-436 to Gly-441, Lys-467 to Leu-478, Phe-497 to Ser-508, Met-550 to Gly-560, Glu-688 to Thr-697, Ile-711 to Gly-720, Ala-747 to Gly-759, Leu-785 to Phe-791, Ser-795 to Gln-800, Thr-808 to Lys-813, Ser-821 to Phe-832, Thr-879 to Glu-889, Leu-898 to Gln-904, Gln-934 to Met-941.	H0521: 4, L0454: 2, S0442: 2, L0758: 2, H0720: 1, H0255: 1, S0376: 1, H0486: 1, H0581: 1, H0373: 1, H0268: 1, S0440: 1, L0763: 1, L0803: 1, H0435: 1, H0658: 1, L3833: 1, H0522: 1, L0748: 1, L0749: 1, L0588: 1 and H0543: 1.		
	HDPBA28	866429	281	69 - 2894	675	Gln-33 to Trp-49, Gly-161 to Gly-172, Ile-207 to Arg-212, Asn-414 to Val-419, Val-423 to Gln-428, Val-436 to Gly-441, Lys-467 to Leu-478, Phe-497 to Ser-508,			







									L5565: 1, L0800: 1, L0764: 1, L0648: 1, L0768: 1, L0774: 1, L0776: 1, L0657: 1, L0559: 1, L0519: 1, L0789: 1, L0792: 1, L0666: 1, L0664: 1, L0709: 1, L3811: 1, H0520: 1, H0547: 1, S0328: 1, S0378: 1, H0754: 1, S0152: 1, H0521: 1, S0190: 1, S0406: 1, H0436: 1, L0748: 1, L0780: 1, L0759: 1, L0601: 1, L0366: 1 and H0423: 1.			
	HDPCL63	847045	284	260 - 733	678	Lys-72 to Cys-80, Leu-90 to Pro-96, Ala-110 to Thr-119, Glu-121 to Gly-128, Ser-140 to Lys-147.						
	HDPCL63	897484	285	605 - 961	679	Pro-8 to Gln-13, Thr-38 to Pro-46, Pro-100 to Met-108, Pro-113 to Pro-118.						
50	HDPCO25	460682	60	182 - 343	454	Pro-22 to His-33, Ser-42 to Trp-48.	H0521: 2, H0445: 2, H0394: 1, H0747: 1, H0581: 1, L0761: 1 and L0750: 1.					
51	HDPGT01	771583	61	8 - 271	455	Cys-65 to Ser-71.	H0521: 3, S0278: 2, S0222: 2, H0284: 2, H0265: 1, H0728: 1, S0007: 1, H0208: 1,	16				

									H0586: 1, H0497: 1, H0642: 1, H0581: 1, H0052: 1, H0572: 1, H0024: 1, H0292: 1, H0428: 1, H0628: 1, H0135: 1, H0163: 1, H0433: 1, S0002: 1, L2263: 1, L0438: 1, L3829: 1, H0539: 1, S0027: 1, S0032: 1, L0439: 1, S0436: 1, S0458: 1 and H0352: 1.			
52	HDPHI51	460679	62	245 - 367	456	Gly-2 to Glu-7, Arg-27 to Gly-34.			H0521: 1			
53	HDPJM30	879325	63	59 - 1633	457	Arg-15 to Val-22.			L0800: 4, H0617: 3, H0521: 3, L0070: 3, L0742: 3, L0770: 2, L0771: 2, L0794: 2, H0689: 2, L0741: 2, L0439: 2, H0445: 2, H0224: 1, H0637: 1, H0370: 1, H0250: 1, H0052: 1, H0194: 1, L0455: 1, S0422: 1, L0761: 1, L0764: 1, L0806: 1, L0659: 1, L5622: 1, L0789: 1, L0790: 1, L0792: 1, H0672: 1, S0152: 1, S0434: 1 and S0436: 1.			
	HDPJM30	603517	286	259 - 438	680	Pro-41 to Ala-55.						
54	HDPND46	637586	64	15 - 1469	458	Ala-107 to Ser-112.			H0522: 2 and L0055: 1.			
55	HDPOJ08	731863	65	159 - 527	459	Lys-30 to Thr-35.			S0474: 29, L0766: 11,			

						H0521: 10, L0803: 7, L0748: 6, L0717: 5, L0759: 5, S0003: 4, L3832: 4, H0663: 3, H0156: 3, L0598: 3, L0770: 3, L0771: 3, L0804: 3, L2439: 3, H0522: 3, L0731: 3, S0436: 3, H0486: 2, S0426: 2, L0805: 2, L0659: 2, L2260: 2, S0126: 2, S0406: 2, L0749: 2, L0755: 2, L0757: 2, L0758: 2, L0590: 2, S0026: 2, H0716: 1, H0341: 1, S0212: 1, L0481: 1, S0444: 1, S0360: 1, L3649: 1, H0637: 1, H0580: 1, H0734: 1, H0749: 1, L3092: 1, H0619: 1, L3388: 1, H0586: 1, H0574: 1, H0427: 1, L0021: 1, H0575: 1, H0318: 1, H0545: 1, H0024: 1, H0373: 1, H0071: 1, H0179: 1, S0214: 1, H0428: 1, H0674: 1, H0591: 1, H0616: 1, H0488: 1, H0494: 1, S0438: 1, S0440: 1, H0647: 1, S0142: 1,					
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									UNKWN: 1, L0369: 1, L0763: 1, L0769: 1, L0646: 1, L0648: 1, L0662: 1, L0650: 1, L0775: 1, L0653: 1, L0776: 1, L0656: 1, L0782: 1, L0809: 1, L0519: 1, S0052: 1, L2657: 1, H0144: 1, L3823: 1, H0520: 1, H0547: 1, H0660: 1, S0380: 1, L0742: 1, L0439: 1, L0750: 1, L0777: 1, S0031: 1, H0445: 1, S0434: 1, H0665: 1, H0667: 1, S0194: 1, S0276: 1 and S0458: 1.				
56	HDPPN86	1037893	66	127 - 267	460				H0542: 4, S0418: 3, H0543: 3, S0038: 2, H0341: 1, L0018: 1, H0069: 1, H0090: 1, H0056: 1, H0494: 1, H0522: 1 and H0423: 1.				
	HDPPN86	895711	287	117 - 257	681								
57	HDPSB18	1043263	67	123 - 323	461	Lys-23 to Lys-31, Ala-38 to Ser-43.			L0769: 5, L0774: 3, H0656: 2, S0442: 2, S0358: 2, S0360: 2, S0278: 2, H0620: 2, L0500: 2, L0775: 2, L0710: 2, L0777: 2, L0752: 2, L0588: 2, H0149: 1, H0295: 1.	10			

									T0049: 1, H0381: 1, H0484: 1, H0483: 1, H0638: 1, S0420: 1, S0444: 1, S0408: 1, S0045: 1, H0587: 1, H0318: 1, H0204: 1, H0530: 1, H0545: 1, H0178: 1, L0471: 1, L0142: 1, H0181: 1, H0087: 1, H0412: 1, H0623: 1, H0100: 1, S0438: 1, H0633: 1, H0646: 1, H0529: 1, L0506: 1, L0761: 1, L0764: 1, L0648: 1, L0766: 1, L0497: 1, L0493: 1, L0511: 1, L0665: 1, L2260: 1, H0698: 1, H0690: 1, H0521: 1, S0406: 1, S3014: 1, L0747: 1, L0780: 1, H0543: 1 and H0422: 1.					
	HDPSB18	903816	288	116 - 307	682									
	HDPSB18	905414	289	1525 - 1566	683									
	HDPSB18	732097	290	345 - 665	684	Lys-57 to Gly-64.								
58	HDPSH53	1309174	68	158 - 430	462	Met-1 to Trp-6, Leu-22 to Thr-27, Pro-44 to Thr-63.	L0804: 2, H0521: 2, L0021: 1, H0617: 1, H0623: 1, L0648: 1 and L0665: 1.							
	HDPSH53	1040056	291	153 - 536	685	Met-1 to Trp-6, Leu-22 to Thr-27, Pro-44 to Gly-58,								

							Ala-61 to Glu-74, Pro-99 to Gly-111, Cys-121 to Ser-127.				
	HDP SH53	882768	292	212 - 484	686		Met-1 to Trp-6, Leu-22 to Thr-27.				
59	HDP SP01	1352280	69	184 - 2313	463		Gln-75 to Cys-80, Glu-97 to Lys-104, Glu-114 to Ala-119, Thr-177 to Gln-190, Asn-230 to Trp-240, Glu-269 to Arg-274, Pro-279 to Ala-286, Pro-323 to Cys-328, Asn-362 to Leu-367, Thr-390 to Arg-397, Leu-490 to Arg-495, Gln-556 to Leu-561, Gln-657 to Val-674.	L0769: 6, L0751: 5, L0752: 5, H0617: 4, L0806: 4, L0731: 4, L0771: 3, L0774: 3, H0370: 2, S0314: 2, H0551: 2, H0059: 2, L0792: 2, L0745: 2, L0750: 2, L0777: 2, S0444: 1, H0728: 1, S0132: 1, H0550: 1, H0392: 1, H0586: 1, H0427: 1, H0618: 1, H0052: 1, H0545: 1, H0123: 1, H0620: 1, S0051: 1, H0135: 1, H0100: 1, H0494: 1, L0800: 1, L0764: 1, L0804: 1, L0775: 1, L0805: 1, L0783: 1, L0809: 1, L0666: 1, L0665: 1, H0684: 1, S0328: 1, H0521: 1, H0555: 1, H0478: 1, L0743: 1, L0747: 1, L0779: 1, L0780: 1, L0755: 1 and S0434: 1.			
	HDP SP01	689129	293	227 - 1153	687		Gln-75 to Cys-80.				
60	HDP SP54	744440	70	2356 - 2499	464		Pro-29 to Lys-37.	L0740: 8, L0662: 3,			

									L0659: 3, L0663: 3, S0422: 2, L0646: 2, L0766: 2, L0439: 2, L0779: 2, H0171: 1, S6024: 1, S0110: 1, S0360: 1, H0411: 1, H0455: 1, S0474: 1, H0510: 1, S0438: 1, L0637: 1, L5565: 1, L0771: 1, L0773: 1, L0794: 1, L0804: 1, L0787: 1, L0665: 1, L0438: 1, H0521: 1, S0406: 1, L0754: 1, L0755: 1 and L0758: 1.			
61	HDPSP54 HDPUH26	502472 866433	294 71	179 - 343 90 - 1739	688 465	Ser-28 to Phe-33, Glu-35 to Pro-41, Lys-48 to Val-54, Pro-100 to Glu-105, Pro-107 to Glu-112, Leu-119 to Gln-125, Gly-335 to Leu-340, Ser-383 to Arg-396, Leu-417 to Lys-429, Asp-477 to Arg-482, Tyr-532 to Ser-540, Ile-542 to Asn-549.	S0358: 4, S0280: 3, H0717: 2, H0370: 2, H0510: 2, H0556: 1, H0716: 1, S0442: 1, S0354: 1, S0476: 1, H0393: 1, H0549: 1, H0586: 1, T0082: 1, H0036: 1, H0590: 1, H0596: 1, H0050: 1, H0628: 1, H0264: 1, H0494: 1, H0509: 1, L2257: 1, L2654: 1, H0521: 1, L0741: 1, L0439: 1, H0445: 1, S0436: 1, L0605: 1, S0011: 1 and H0665: 1.					
62	HDPUW68	812737	72	40 - 1440	466	Gly-12 to Tyr-26,	H0677: 47, H0521: 14,					

						Val-52 to Asp-59, Gln-88 to Asp-93, Arg-124 to Asn-129, His-193 to Arg-198, Gln-207 to Thr-213, Gln-338 to Arg-346, Ser-378 to Ala-384, Ser-413 to Arg-420, Ser-428 to Glu-434, His-443 to Ser-451, Glu-454 to Ser-461.		H0295: 3, H0587: 3, H0556: 2, H0656: 2, H0638: 2, H0411: 2, S0002: 2, L0766: 2, L0776: 2, L0659: 2, L0809: 2, H0670: 2, H0522: 2, S0404: 2, L0743: 2, L0744: 2, L0740: 2, L0731: 2, S0134: 1, H0657: 1, H0254: 1, S0476: 1, S0278: 1, H0486: 1, H0575: 1, H0606: 1, H0135: 1, H0561: 1, S0438: 1, L0761: 1, L0768: 1, L0655: 1, L2261: 1, S0374: 1, H0690: 1, H0435: 1, H0658: 1, H0696: 1, H0678: 1, L0779: 1, L0752: 1, H0445: 1, S0434: 1 and S0436: 1.		
63	HDPWU34	630354	73	117 - 1091	467	Arg-23 to Gln-30, Asp-37 to Asp-50, Glu-230 to Met-235, Pro-271 to Arg-281, Arg-306 to Ser-316, Ser-318 to Gly-325.		S0278: 3, H0641: 3, S0142: 3, L0770: 3, H0521: 3, H0271: 2, L0794: 2, L0748: 2, L0777: 2, L0599: 2, H0583: 1, H0650: 1, H0657: 1, H0656: 1, H0663: 1, H0638: 1, S0358: 1, S0376: 1, H0545: 1, S0388: 1, H0594: 1, L2270: 1,		



								S0144: 1, S0344: 1, L0763: 1, L0646: 1, L0648: 1, L0767: 1, L0766: 1, L0650: 1, L0775: 1, L0787: 1, L0664: 1, S0216: 1, H0576: 1, H0727: 1, L0756: 1, L0757: 1, S0260: 1 and S0436: 1.			
	HDPWU34	701979	295	111 - 245	689	Arg-25 to Ser-35, Ser-37 to Gly-44.					
64	HDPXY01	879048	74	23 - 319	468	Pro-39 to Trp-44.		L0646: 4, L0666: 4, L0662: 3, L0749: 3, H0661: 2, H0620: 2, H0617: 2, H0144: 2, L0777: 2, L0731: 2, H0170: 1, S0360: 1, S0046: 1, L0717: 1, H0013: 1, H0052: 1, H0039: 1, H0622: 1, H0606: 1, H0673: 1, L0769: 1, L0796: 1, L5565: 1, L5566: 1, L0764: 1, L0648: 1, L0381: 1, L0805: 1, L0659: 1, L0789: 1, L0792: 1, L0663: 1, L0665: 1, H0689: 1, H0660: 1, H0648: 1, H0539: 1, H0521: 1, L0779: 1 and L0603: 1.	17		
	HDPXY01	904768	296	33 - 329	690	Pro-39 to Trp-44.					
	HDPXY01	895716	297	539 - 607	691						

	HDPXY01	895715	298	1190 - 1267	692				
65	HDTBV77	785879	75	326 - 2149	469	Lys-5 to Lys-10, Asn-33 to Lys-39, Asp-48 to Lys-54, Pro-62 to Asp-67, Asn-116 to Arg-123, His-157 to Ala-162, Val-242 to Lys-249, Val-251 to Asp-264.	Lys-5 to Lys-10, Asn-33 to Lys-39, Asp-48 to Lys-54, Pro-62 to Asp-67, Asn-116 to Arg-123, His-157 to Ala-162, Val-242 to Lys-249, Val-251 to Asp-264.	H0553: 3, H0717: 2, H0486: 1, H0427: 1, H0081: 1, H0014: 1, S0388: 1, H0112: 1, H0030: 1, H0031: 1, H0644: 1, H0488: 1, H0519: 1, L0759: 1, H0543: 1 and H0506: 1.	
66	HDTDQ23	1306984	76	132 - 302	470	Arg-24 to Arg-31, Ile-33 to Trp-41, Met-43 to His-52.	Arg-24 to Arg-31, Ile-33 to Trp-41, Met-43 to His-52.	L0659: 5, L0666: 4, L0665: 4, L2634: 3, L0471: 2, H0031: 2, L0646: 2, L0794: 2, L0766: 2, L0657: 2, H0265: 1, H0685: 1, L0785: 1, S0356: 1, S0376: 1, S0360: 1, H0742: 1, S0007: 1, H0747: 1, H0486: 1, L2540: 1, H0069: 1, H0025: 1, H0457: 1, H0252: 1, H0428: 1, L0055: 1, H0038: 1, S0344: 1, L0625: 1, L0761: 1, L0800: 1, L0553: 1, L0649: 1, L0803: 1, L0650: 1, L0606: 1, L3872: 1, L0791: 1, L0663: 1, L0664: 1, H0684: 1, H0435: 1, H0648: 1, S0380: 1, L3832: 1, L0749: 1, L0786: 1,	

									L0780: 1, L0755: 1, L0759: 1, L0596: 1, L0601: 1, H0543: 1 and H0422: 1.			
	HDTDQ23	879009	299	148 - 471	693			Arg-24 to Arg-31, Ile-33 to Gly-41.				
	HDTDQ23	751707	300	148 - 369	694			Arg-24 to Arg-31.				
67	HE2DE47	619852	77	808 - 2427	471			Leu-9 to Tyr-15, Asp-34 to Gln-46, Pro-51 to Asp-57, Gly-88 to Thr-104, Thr-123 to Ser-128.	L0439: 10, L0747: 9, L0766: 8, L0770: 5, L0666: 4, L0754: 4, L0777: 4, L0659: 3, L0783: 3, S0126: 3, H0543: 3, L0483: 2, H0264: 2, L0764: 2, L0662: 2, L0768: 2, L0665: 2, L0438: 2, L0748: 2, L0756: 2, L0752: 2, L0755: 2, L0758: 2, L0759: 2, H0170: 1, T0049: 1, H0341: 1, S0029: 1, H0661: 1, H0306: 1, S0408: 1, H0580: 1, S0045: 1, H0431: 1, H0455: 1, H0586: 1, L0622: 1, H0575: 1, H0004: 1, H0581: 1, H0421: 1, H0263: 1, H0569: 1, H0015: 1, S0051: 1, S0003: 1, H0615: 1, L0142: 1, H0090: 1, H0625: 1, S0422: 1, L0598: 1,			

									H0529: 1, L0769: 1, L0667: 1, L0646: 1, L0774: 1, L0375: 1, L0657: 1, L0519: 1, L0664: 1, H0144: 1, S0374: 1, H0547: 1, H0435: 1, H0666: 1, S0380: 1, H0521: 1, S0404: 1, H0555: 1, L0749: 1, L0750: 1, L0779: 1, L0592: 1, L0608: 1, S0026: 1 and H0542: 1.			
	HE2DE47	382025	301	515 - 757	695	Leu-31 to Asn-38.						
68	HE2NV57	740750	78	99 - 398	472	Ala-84 to Gln-93.			S0414: 3, L0805: 3, S0412: 3, H0457: 2, L0756: 2, H0170: 1, H0645: 1, H0455: 1, H0421: 1, H0100: 1, L0803: 1, S0052: 1, S0374: 1, H0696: 1 and L0743: 1.			
69	HE2PH36	570903	79	28 - 228	473				H0171: 1, S0114: 1 and S0356: 1.			
70	HE8DS15	847060	80	91 - 309	474				L0779: 8, L0770: 7, L0731: 7, L0662: 6, L0803: 5, L0599: 5, L0758: 4, H0739: 3, H0624: 3, H0486: 3, H0615: 3, L0748: 3, L0750: 3, H0713: 2, S0222: 2, H0575: 2, H0050: 2, H0031: 2,			

					H0553: 2, S0036: 2, H0038: 2, S0422: 2, L0804: 2, L0774: 2, L0775: 2, L0647: 2, L0438: 2, L0742: 2, L0743: 2, L0747: 2, L0777: 2, L0605: 2, L0485: 2, H0171: 1, H0717: 1, S0442: 1, H0208: 1, H0411: 1, H0586: 1, H0587: 1, L3655: 1, H0013: 1, H0156: 1, H0108: 1, H0581: 1, S0049: 1, H0194: 1, H0572: 1, H0123: 1, L0471: 1, H0024: 1, H0373: 1, S0051: 1, S6028: 1, H0188: 1, H0644: 1, H0628: 1, H0383: 1, H0316: 1, T0067: 1, L0768: 1, L0794: 1, L0375: 1, L0806: 1, L0659: 1, L0532: 1, L0665: 1, H0144: 1, H0691: 1, S0126: 1, H0660: 1, H0648: 1, S0328: 1, S0378: 1, S0380: 1, H0436: 1, S0028: 1, L0749: 1, L0756: 1, L0759: 1, H0444: 1, S0242: 1 and H0352: 1.
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71	HE9CO69	596829	81	161 - 286	475	Asn-23 to Val-37.	L0439: 11, L0770: 10, L0483: 8, L2918: 7, S0422: 6, L0752: 6, L3432: 5, L0754: 5, L0759: 5, S0212: 4, S0003: 4, H0674: 4, L0769: 4, L0663: 4, L0757: 4, H0494: 3, L0794: 3, L0803: 3, L0805: 3, L0750: 3, H0423: 3, S0045: 2, S0046: 2, L3722: 2, L0021: 2, S0214: 2, H0644: 2, H0551: 2, H0633: 2, L0598: 2, L0804: 2, L0775: 2, L0776: 2, L0666: 2, H0144: 2, H0659: 2, S0404: 2, L0743: 2, L0748: 2, L0756: 2, L0777: 2, S0242: 2, H0556: 1, T0002: 1, H0686: 1, L0002: 1, L0785: 1, L3814: 1, H0662: 1, L2281: 1, S0420: 1, S0376: 1, H0580: 1, S0007: 1, L3058: 1, H0619: 1, L2255: 1, L3655: 1, T0060: 1, T0114: 1, S0280: 1, H0156: 1, H0575: 1, S0010: 1, H0546: 1, H0545: 1,		
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									H0457: 1, H0178: 1, L0471: 1, H0014: 1, S0388: 1, S0051: 1, H0375: 1, H0039: 1, H0553: 1, H0169: 1, S0036: 1, H0090: 1, T0067: 1, H0264: 1, H0429: 1, S0440: 1, S0144: 1, H0529: 1, L0638: 1, L0773: 1, L0774: 1, L0378: 1, L0659: 1, L0526: 1, L5623: 1, L0791: 1, L0792: 1, L0793: 1, L0665: 1, L2653: 1, L2257: 1, L2260: 1, H0702: 1, L0438: 1, H0520: 1, H0547: 1, H0519: 1, S0122: 1, H0690: 1, S0380: 1, S0152: 1, H0521: 1, H0627: 1, L0740: 1, L0758: 1, S0436: 1, L0592: 1, S0011: 1, H0653: 1, S0196: 1 and H0721: 1.					
72	HE9HY07	420063	82	35 - 160	476	Pro-35 to Phe-41.	H0615: 1 and H0144: 1.							
73	HE9OW20	1352337	83	129 - 1193	477	Gln-44 to Gly-51, Gln-119 to Ala-124, Trp-209 to Ile-223.	H0570: 1, S0210: 1, L0792: 1, H0144: 1, L0595: 1, H0543: 1 and L0690: 1.							
	HE9OW20	838598	302	136 - 1074	696	Gln-44 to Gly-51, Gln-119 to Ala-124,								





									H0684: 1, H0659: 1, H0658: 1, H0660: 1, H0648: 1, H0672: 1, S0380: 1, H0518: 1, H0696: 1, S0027: 1, L0744: 1, L0745: 1, L0780: 1, L0752: 1, L0757: 1, S0436: 1, L0592: 1, S0026: 1, H0542: 1, H0543: 1 and H0422: 1.			
75	HEOMQ63	603533	85	123 - 266	479				L0766: 3, L0777: 2, S0116: 1, S0376: 1, H0457: 1, S0440: 1, L0771: 1, L0803: 1, L0804: 1, L0657: 1, L0659: 1, H0525: 1, S0406: 1 and L0750: 1. H0150: 1			
76	HEPAB80	1307790	86	73 - 438	480	Met-1 to Pro-6, Glu-58 to Cys-63, Glu-65 to Gly-72, Thr-74 to Asn-88, Tyr-104 to Trp-109.						
	HEPAB80	570048	304	67 - 435	698	Met-1 to Pro-6, Glu-58 to Cys-63, Glu-65 to Gly-72, Thr-74 to Val-87.						
77	HFABG18	847073	87	53 - 316	481	Glu-36 to Lys-55.			L0743: 7, L0747: 6, L0758: 6, L0766: 5, L0666: 5, L0754: 5, L0750: 5, L0662: 4, L0783: 4, L0665: 4, L0751: 4, L0777: 4,			

					H0170: 3, S0132: 3, L0503: 3, L0500: 3, L0769: 3, L0774: 3, L0805: 3, L0809: 3, L0565: 3, L0749: 3, L0757: 3, L0596: 3, S0360: 2, H0013: 2, H0024: 2, H0617: 2, H0673: 2, L0641: 2, L0773: 2, L0768: 2, L0649: 2, L0499: 2, L0375: 2, L0659: 2, L0664: 2, H0658: 2, L0744: 2, L0748: 2, L0740: 2, L0745: 2, L0603: 2, H0265: 1, H0556: 1, S6024: 1, H0661: 1, H0662: 1, S0418: 1, T0008: 1, H0351: 1, S0222: 1, H0370: 1, T0039: 1, L0015: 1, S0280: 1, H0575: 1, H0004: 1, H0618: 1, H0596: 1, H0231: 1, H0545: 1, H0009: 1, H0012: 1, S0388: 1, S0051: 1, H0292: 1, H0688: 1, H0644: 1, L0055: 1, H0674: 1, H0124: 1, H0598: 1, H0087: 1, S0440: 1, S0150: 1, S0142: 1, L0763: 1,	
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									L0770: 1, L0764: 1, L0771: 1, L0794: 1, L0650: 1, L0651: 1, L0378: 1, L0776: 1, L0655: 1, L0629: 1, L0657: 1, L0493: 1, L0634: 1, L0528: 1, H0144: 1, H0547: 1, H0690: 1, H0682: 1, H0670: 1, S0328: 1, H0518: 1, H0436: 1, L0746: 1, L0756: 1, L0779: 1, L0780: 1, L0731: 1, H0445: 1, S0434: 1, L0592: 1, L0595: 1, H0668: 1, S0194: 1, H0506: 1 and H0008: 1.			
78	HFABH95	566712	88	199 - 549	482				S6024: 1, S0430: 1, H0039: 1, H0056: 1 and H0660: 1.			
79	HFAEF57	534142	89	232 - 492	483			Leu-69 to Leu-74.	S6024: 1			
80	HFCEB37	411345	90	487 - 519	484				S0222: 2, L0438: 2, S0134: 1, S0045: 1, H0747: 1, H0013: 1, H0009: 1, S6028: 1, L0598: 1, L0532: 1, S0052: 1, H0696: 1, S0146: 1, L0439: 1, L0777: 1 and L0366: 1.			
81	HFFAD59	520369	91	44 - 181	485			Lys-13 to Asn-19, Asn-27 to Asn-35.	H0172: 2			
82	HFGAD82	513669	92	1019 - 1135	486				L0439: 22, L0756: 12,			



									L0777: 1, L0758: 1, L0592: 1 and L0593: 1.			
83	HFIIN69	1011487	93	45 - 176	487				S0222: 1, S0152: 1, L0759: 1 and S0194: 1.	15		
	HFIIN69	844413	305	52 - 183	699							
	HFIIN69	874248	306	280 - 288	700							
84	HFIUR10	532060	94	50 - 184	488		Gln-31 to Pro-39.		H0265: 2, L0591: 2, H0556: 1, S0356: 1, H0271: 1, H0622: 1, S0428: 1, S0434: 1 and S0196: 1.			
85	HFKEFG02	634743	95	110 - 271	489				L0803: 5, L0439: 2, H0431: 1, H0012: 1, T0010: 1, H0063: 1 and L0774: 1.			
86	HFTBM50	545012	96	158 - 262	490		Ala-19 to Lys-34.		L0439: 6, L0731: 4, L0769: 2, L0666: 2, S0432: 2, S0206: 2, L0751: 2, L0777: 2, L0759: 2, L0591: 2, H0341: 1, H0661: 1, S0408: 1, H0601: 1, H0497: 1, H0123: 1, L0471: 1, H0051: 1, H0252: 1, H0673: 1, H0616: 1, H0551: 1, H0646: 1, S0422: 1, L0372: 1, L0771: 1, L0773: 1, L0768: 1, L0775: 1, L0375: 1, L0527: 1, L0664: 1, L0665: 1, S0374: 1, H0519: 1, H0659: 1,			

								H0521: 1, H0522: 1, L0747: 1, L0749: 1, L0755: 1, L0758: 1, S0031: 1, L0683: 1, L0590: 1 and L0595: 1.			
87	HFTDZ36	545726	97	547 - 753	491			L0779: 5, L0758: 4, S0036: 2, H0038: 2, S0422: 2, L0662: 2, L0803: 2, H0171: 1, H0208: 1, H0411: 1, S0222: 1, H0013: 1, H0108: 1, H0581: 1, H0123: 1, H0024: 1, H0373: 1, S0051: 1, S6028: 1, H0615: 1, L0794: 1, L0804: 1, S0126: 1, H0436: 1, S0028: 1, L0756: 1, L0777: 1, L0731: 1 and S0242: 1.			
88	HFXBL33	778070	98	152 - 640	492			H0657: 3, H0645: 2, L0748: 2, H0542: 2, H0583: 1, H0650: 1, S0001: 1, L0586: 1, H0013: 1, L0021: 1, T0071: 1, H0354: 1, H0179: 1, T0006: 1, H0591: 1, H0272: 1, L0667: 1, H0547: 1, H0521: 1, S0404: 1, S0031: 1 and L0599: 1.			
89	HFXHK73	609826	99	247 - 450	493	His-55 to His-67.		S0001: 1			
90	HFXJX44	701988	100	98 - 241	494			H0590: 2, S0282: 1,			

									H0486: 1, H0421: 1 and H0594: 1.			
91	HFXKY27	634161	101	44 - 220	495		Lys-23 to Lys-35, Met-46 to Tyr-52.		H0257: 49, H0256: 15 and S0282: 1.			
92	HGBHI35	570262	102	87 - 965	496		Pro-10 to Arg-15, Leu-96 to Ser-103, Gly-172 to Pro-178, Gln-213 to Asp-218, Asn-268 to Leu-275, Arg-282 to Phe-289.		L0748: 9, L0766: 6, L0665: 6, L0751: 6, H0550: 5, S0358: 4, L0774: 4, L0758: 4, L0581: 4, H0135: 3, L0662: 3, L0775: 3, L0776: 3, L0743: 3, L0747: 3, L0749: 3, L0777: 3, L0600: 3, H0295: 2, H0722: 2, H0052: 2, H0014: 2, H0510: 2, L0640: 2, L0659: 2, L0526: 2, L0809: 2, H0696: 2, L0753: 2, S0134: 1, S0212: 1, S0376: 1, S0408: 1, H0742: 1, H0730: 1, H0747: 1, H0549: 1, H0331: 1, H0486: 1, H0575: 1, S0049: 1, H0085: 1, H0204: 1, H0057: 1, S0051: 1, H0266: 1, H0188: 1, H0687: 1, H0169: 1, H0090: 1, H0591: 1, T0067: 1, H0488: 1, H0714: 1, S0438: 1, L0374: 1, L0648: 1, L0376: 1,			

93	HGLAF75	566838	103	231 - 596	497	Ser-40 to Gly-45, Leu-73 to Arg-80.	L0807: 1, L5622: 1, L0790: 1, L0791: 1, L0666: 1, H0701: 1, H0547: 1, S0126: 1, H0660: 1, H0672: 1, H0539: 1, H0436: 1, L0439: 1, L0746: 1, L0750: 1, L0779: 1, L0752: 1, L0759: 1 and S0436: 1.			
94	HHBCS39	1003028	104	104 - 604	498	Ser-25 to Ala-30, Gln-36 to Thr-48, Arg-53 to Asn-67, Glu-82 to Phe-93, Ser-134 to Asn-142.	H0351: 10, L0439: 4, L0766: 3, L3255: 2, L2562: 2, L0775: 2, L0666: 2, L0779: 2, L0780: 2, L0755: 2, L0731: 2, H0772: 1, L3388: 1, H0333: 1, H0486: 1, H0015: 1, H0687: 1, S0422: 1, L0761: 1, L0776: 1, L0659: 1, L0663: 1, H0682: 1, S0152: 1, L0745: 1, L0752: 1 and S0026: 1.	6		



									H0457: 1, H0123: 1, H0050: 1, H0373: 1, H0551: 1, H0102: 1, S0438: 1, L0775: 1, L0790: 1 and L0754: 1.			
	HHBCS39	883427	307	150 - 650	701	Ser-25 to Ala-30, Gln-36 to Thr-48, Arg-53 to Asn-67, Glu-82 to Phe-93, Ser-134 to Asn-142.						
	HHBCS39	847543	308	1260 - 1340	702							
95	HHEAA08	638231	105	88 - 324	499	Asp-9 to Gln-17.			H0341: 1 and H0542: 1.			
	HHEAA08	623588	309	311 - 373	703							
96	HHENV10	562772	106	143 - 295	500	Asp-26 to Leu-36, Leu-42 to Phe-50.			H0543: 2, H0497: 1 and H0625: 1.			
97	HHFFJ48	634521	107	65 - 385	501	Ser-19 to Ser-25, Pro-27 to Gly-33, Pro-40 to Asn-47, Pro-65 to Gln-70.			H0580: 1 and H0050: 1.			
98	HHFHJ59	411332	108	192 - 530	502	Pro-32 to Ser-39.			L0748: 9, H0620: 6, L0439: 6, L0766: 5, L0774: 5, H0657: 4, L0758: 4, S0358: 3, H0617: 3, L0740: 3, L0747: 3, L0752: 3, S0360: 2, S0278: 2, H0492: 2, H0150: 2, H0102: 2, L0769: 2, L0662: 2, L0806: 2, L0527: 2, H0696: 2, S3014: 2, L0756: 2, L0755: 2, L0731: 2, L0759: 2, L0591: 2,			

						H0422: 2, H0556: 1, H0295: 1, H0656: 1, H0341: 1, H0661: 1, S0418: 1, S0420: 1, S0356: 1, S0410: 1, L0717: 1, H0575: 1, H0318: 1, H0421: 1, S0049: 1, H0597: 1, H0545: 1, H0050: 1, H0012: 1, L0492: 1, H0239: 1, H0594: 1, H0424: 1, H0181: 1, H0165: 1, H0413: 1, H0059: 1, L0370: 1, S0294: 1, S0422: 1, H0529: 1, L0763: 1, L0770: 1, L0639: 1, L0771: 1, L0773: 1, L0767: 1, L0768: 1, L0775: 1, L0651: 1, L0376: 1, L0776: 1, L0655: 1, L0657: 1, L0659: 1, L0542: 1, L0526: 1, L0783: 1, L0809: 1, L0529: 1, L0663: 1, L0665: 1, H0144: 1, S0374: 1, H0693: 1, L0438: 1, S0330: 1, S0380: 1, H0134: 1, L0749: 1, L0750: 1, L0786: 1, L0777: 1, H0543: 1 and S0452: 1.				
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99	HHGBO91	520198	109	140 - 289	503	Lys-39 to Glu-45.	H0333: 1, H0597: 1 and H0670: 1.		
100	HHGCG53	340818	110	230 - 361	504		H0333: 1	8	
101	HHGCM76	662329	111	270 - 536	505		L0803: 6, H0052: 4, H0036: 3, L0665: 3, H0574: 2, H0559: 2, L0763: 2, L0809: 2, L0791: 2, L0666: 2, L0663: 2, L0748: 2, L0745: 2, L0747: 2, H0624: 1, H0265: 1, H0657: 1, H0381: 1, S0045: 1, H0550: 1, H0614: 1, H0587: 1, H0333: 1, T0040: 1, L0022: 1, H0575: 1, H0564: 1, H0068: 1, H0509: 1, L0769: 1, L0637: 1, L0643: 1, L0764: 1, L0662: 1, L0804: 1, L0806: 1, L0527: 1, L0783: 1, L0382: 1, L0664: 1, H0144: 1, H0690: 1, H0682: 1, H0670: 1, H0694: 1, H0626: 1, L0743: 1, L0777: 1, L0780: 1, L0755: 1, H0343: 1 and S0011: 1.	17	
	HHGCM76	383547	310	270 - 302	704				
102	HHGCQ54	544615	112	62 - 217	506	Ser-16 to Val-33.	L0439: 9, S0434: 8, L0637: 3, L0780: 3, L0662: 2, L0790: 2,		



									H0251: 1, H0327: 1, H0545: 1, H0046: 1, L0471: 1, S0051: 1, H0375: 1, H0622: 1, T0006: 1, H0553: 1, H0598: 1, H0163: 1, H0040: 1, H0551: 1, L0564: 1, H0334: 1, H0561: 1, S0440: 1, H0529: 1, L0800: 1, L0794: 1, L0651: 1, L0805: 1, L0655: 1, L0606: 1, L0527: 1, L0635: 1, L0382: 1, L0809: 1, L0792: 1, L0663: 1, S0216: 1, H0144: 1, H0520: 1, H0519: 1, S0328: 1, S0380: 1, S0404: 1, H0436: 1, S0392: 1, S0028: 1, L0745: 1, L0779: 1, L0777: 1, L0752: 1, S0260: 1, L0480: 1, S0026: 1, H0665: 1, S0192: 1, S0194: 1, H0423: 1, S0424: 1 and H0506: 1.			
104	HJABB94	456466	114	74 - 307	508	Ala-28 to His-41, Pro-43 to Gln-64.			H0624: 1, S0360: 1, H0586: 1, L0021: 1, T0041: 1 and L0779: 1.			
105	HJACG02	1307789	115	66 - 392	509	Val-54 to Asp-59.			S0442: 4, L0764: 4, S0408: 3, H0306: 2, H0263: 2, H0596: 2,			





									L0754: 2, L0747: 2, L0749: 2, L0757: 2, S0356: 1, S0444: 1, S0360: 1, H0013: 1, S0010: 1, H0421: 1, H0263: 1, H0596: 1, L0157: 1, L0471: 1, H0553: 1, H0628: 1, H0090: 1, H0561: 1, S0372: 1, L2270: 1, S0422: 1, L0667: 1, L0768: 1, L0776: 1, L0809: 1, H0658: 1, H0648: 1, S0330: 1, H0521: 1, H0134: 1, S0027: 1, L0748: 1, L0756: 1, L0755: 1, L0731: 1, S0434: 1, L0592: 1 and H0542: 1.			
109	HKABZ65	862030	119	77 - 808	513	Ser-25 to Ala-31, Gln-146 to Ser-151, His-231 to Asn-236.		H0494: 1				
	HKABZ65	665424	314	69 - 800	708	Ser-25 to Ala-31, Gln-146 to Ser-151, His-231 to Asn-236.						
110	HKACD58	1352202	120	38 - 940	514	Thr-42 to Pro-53, Val-78 to Glu-86, Glu-103 to Met-112, Ala-124 to Gly-131, Trp-158 to Glu-168, Gln-189 to Phe-210, Ala-221 to Gly-226, Arg-274 to Asp-284,	S0360: 12, S0436: 3, S0194: 3, S0114: 2, H0483: 2, S0408: 2, L3504: 2, H0575: 2, H0581: 2, S0344: 2, L2262: 2, H0519: 2, L0754: 2, H0139: 1, L2884: 1, H0657: 1,					



						Ala-294 to Gly-299.	H0656: 1, S0420: 1, S0356: 1, S0410: 1, L2333: 1, H0151: 1, S0046: 1, L3127: 1, H0549: 1, H0613: 1, H0427: 1, H0546: 1, H0081: 1, H0355: 1, S0312: 1, H0032: 1, H0383: 1, H0551: 1, H0264: 1, T0042: 1, H0494: 1, H0386: 1, H0509: 1, H0649: 1, S0210: 1, L0646: 1, L0804: 1, L0805: 1, L0809: 1, L5622: 1, L2651: 1, L2265: 1, L2702: 1, H0682: 1, H0435: 1, H0670: 1, H0672: 1, H0521: 1, H0696: 1, H0134: 1, S0206: 1, L0741: 1, L0743: 1, L0744: 1, L0756: 1, L0596: 1, L0581: 1, L0593: 1, L0595: 1, L0366: 1, S0242: 1, S0196: 1, H0423: 1 and H0506: 1.		
	HKACD58	552465	315	35 - 499	709	Thr-42 to Pro-53, Val-78 to Glu-86, Glu-103 to Met-112, Ala-124 to Gly-131.			
111	HKAEV06	1352263	121	501 - 1814	515	Thr-6 to Trp-13, Thr-75 to Gln-80,	L0438: 2, L0758: 2, S0442: 1, S0354: 1,		

						Thr-112 to Tyr-117, Leu-133 to Pro-138, Ala-146 to Phe-153, Gln-319 to Ser-325, Val-354 to His-372, Pro-391 to Gly-396, Val-405 to Thr-412, Ile-425 to Asp-437.	S0444: 1, H0741: 1, L0021: 1, T0082: 1, H0046: 1, H0494: 1, S0440: 1, L3815: 1, L0800: 1, L0662: 1, L5574: 1, L0803: 1, L0776: 1, L0659: 1, L2655: 1, L2653: 1, S0374: 1, H0547: 1, H0672: 1, S0330: 1, H0521: 1, H0696: 1, L0439: 1, L0752: 1, L0594: 1 and H0543: 1.		
	HKAEV06	638238	316	197 - 370	710	Thr-6 to Trp-13.			
112	HKAFT66	946512	122	508 - 831	516	Ser-51 to Thr-57.	S0474: 5, S0422: 3, H0580: 2, S0444: 1, H0494: 1 and H0543: 1.		
	HKAFT66	889258	317	508 - 831	711	Ser-51 to Thr-57.			
	HKAFT66	904790	318	234 - 347	712	Gln-23 to Asp-28.			
113	HKB1E57	876571	123	178 - 879	517	Ser-7 to Pro-14, Arg-47 to Arg-52, His-117 to Val-123, Glu-142 to Thr-149, Leu-162 to Ala-167, Gly-172 to Asn-177, Thr-226 to Ala-232.	L0747: 4, L0766: 3, L0776: 3, L0665: 3, H0328: 2, L0763: 2, L0769: 2, L0772: 2, L0764: 2, L0666: 2, L0745: 2, L0750: 2, L0777: 2, L0759: 2, L0608: 2, H0556: 1, S0116: 1, H0384: 1, S0360: 1, S0408: 1, H0637: 1, H0722: 1, H0735: 1, H0619: 1, H0492: 1, H0156: 1, H0421: 1, H0620: 1,		

									S0051: 1, H0083: 1, H0510: 1, H0266: 1, H0031: 1, H0634: 1, H0560: 1, S0440: 1, H0132: 1, H0695: 1, L0800: 1, L0521: 1, L0662: 1, L0774: 1, L0806: 1, L0807: 1, H0144: 1, H0690: 1, H0658: 1, H0521: 1, H0522: 1, L0439: 1, L0746: 1, L0752: 1, L0480: 1, L0589: 1, L0592: 1, H0543: 1 and H0422: 1.			
	HKB1E57	654871	319	30 - 170	713	Met-1 to Tyr-6, Thr-38 to Ala-44.						
114	HKFBC53	1352286	124	64 - 1473	518	Arg-52 to Ala-58, Thr-121 to Lys-126, Gly-156 to Gln-164, Gly-201 to Glu-215, Thr-432 to Gly-450, Glu-461 to Gly-466.			L0794: 11, H0521: 11, S0002: 8, L0805: 8, L0803: 7, S0278: 6, S0144: 6, L0774: 4, L0777: 4, S0380: 3, H0265: 2, H0556: 2, H0255: 2, H0638: 2, L0761: 2, L0776: 2, L0809: 2, S0406: 2, S0298: 1, S0420: 1, S0356: 1, H0431: 1, H0618: 1, H0546: 1, H0100: 1, H0429: 1, H0494: 1, H0509: 1, S0142: 1, S0426: 1, L0640: 1, L0763: 1,			

								L0770: 1, L3904: 1, L0800: 1, L0804: 1, L0806: 1, L0807: 1, L4669: 1, L5622: 1, L5623: 1, L0791: 1, L0792: 1, L0666: 1, L2261: 1, S0374: 1, H0690: 1, H0522: 1, S0390: 1, L0740: 1, L0751: 1, L0756: 1, L0779: 1 and L0731: 1.			
	HKFBC53	701893	320	41 - 1369	714	Ala-28 to Ala-33, Arg-38 to Leu-48, Thr-120 to Lys-125, Gly-155 to Gln-163, Gly-200 to Glu-214.					
	HKFBC53	513190	321	3 - 929	715	Ala-1 to Gly-6, Ala-10 to Tyr-18.					
	HKFBC53	383426	322	3 - 731	716	Ala-1 to Gly-6, Ala-10 to Tyr-18.					
115	HKGDL36	877489	125	53 - 835	519	Pro-36 to Gly-42, Gly-54 to Arg-65, Ala-85 to Ala-91, Ala-95 to Gln-102, Ala-115 to Pro-121, Pro-166 to Asp-191, Lys-243 to Ala-249.	H0424: 28, L0803: 25, L0805: 9, L0636: 7, L0774: 5, L0770: 4, H0661: 2, S0222: 2, L0157: 2, L0638: 2, L3904: 2, L0776: 2, L0659: 2, L0809: 2, L0789: 2, H0539: 2, L0592: 2, H0295: 1, S0114: 1, H0663: 1, S6026: 1, H0549: 1, H0748: 1, H0571: 1, S0051: 1, T0006: 1,				

									H0033: 1, H0604: 1, H0213: 1, H0418: 1, H0417: 1, H0538: 1, L0769: 1, L3905: 1, L0794: 1, L0647: 1, L0787: 1, H0684: 1, H0672: 1, L0749: 1, L0753: 1, L0759: 1, S0260: 1, S0434: 1 and S0436: 1.				
	HKGDL36	704088	323	55 - 501	717	Pro-36 to Gly-42, Pro-64 to Ala-76, Gly-83 to Ala-90, Ser-100 to Cys-108, Thr-126 to Ser-135.							
116	HKISB57	625956	126	130 - 417	520	Ala-23 to Arg-36, His-38 to Ala-46, Pro-50 to Gly-56, Arg-85 to Val-94.			L0747: 5, L0731: 5, H0031: 4, L0599: 4, S0045: 3, H0411: 3, H0494: 3, L0783: 3, L0743: 3, L0758: 3, L0759: 3, L0604: 3, H0295: 2, S0356: 2, S0360: 2, S0046: 2, H0413: 2, L0774: 2, H0651: 2, S0027: 2, L0748: 2, L0439: 2, L0752: 2, L0601: 2, H0484: 1, S0132: 1, H0586: 1, H0333: 1, H0486: 1, H0042: 1, H0122: 1, H0546: 1, H0041: 1, H0050: 1, H0408: 1, H0288: 1,				

117	HKMMW74	581399	127	202 - 327	521			H0688: 1, H0424: 1, H0644: 1, H0383: 1, L0772: 1, L0764: 1, L0662: 1, L0364: 1, L0653: 1, L0782: 1, L0789: 1, L0666: 1, L0663: 1, L0664: 1, H0144: 1, S0148: 1, H0593: 1, H0666: 1, S0330: 1, S0044: 1, S0037: 1, S3014: 1, L0757: 1, S0031: 1, H0667: 1 and H0506: 1.		
118	HLDNA86	1352197	128	238 - 726	522	Arg-35 to Ala-41, Phe-55 to Arg-61, Lys-152 to His-163.		H0431: 1 L0758: 10, L0731: 8, L0747: 7, H0545: 6, L0769: 6, L0809: 6, L0740: 6, L0803: 5, L0775: 5, L0748: 5, L0755: 5, S0360: 4, L0749: 4, L0757: 4, S0358: 3, H0722: 3, L0771: 3, L0774: 3, L0657: 3, L0782: 3, L0789: 3, T0049: 2, H0638: 2, S0278: 2, H0309: 2, H0266: 2, S0438: 2, H0652: 2, L0770: 2, L0768: 2, L0794: 2, L0518: 2, L0666: 2, S0126: 2, S0027: 2, L0743: 2, L0751: 2, L0756: 2,		



								L0659: 1, L5622: 1, L0663: 1, L0665: 1, H0651: 1, S0044: 1, H0555: 1, S3012: 1, S0390: 1, S3014: 1, L0750: 1, S0026: 1, H0653: 1, S0194: 1, H0543: 1, H0423: 1, S0462: 1 and H0721: 1.			
	HILDNA86	535730	324	45 - 323	718	Arg-35 to Ala-41.					
119	HLDON23	636083	129	368 - 709	523	Arg-28 to Gln-36.		L0805: 8, L0809: 6, L0439: 5, L0777: 5, L0748: 4, L0800: 3, L0662: 3, L0659: 3, L0750: 3, L0758: 3, H0208: 2, H0123: 2, H0617: 2, L0769: 2, L0803: 2, L0776: 2, L0666: 2, L0438: 2, L0780: 2, L0731: 2, L3643: 1, H0741: 1, H0497: 1, L0622: 1, T0109: 1, H0581: 1, L0738: 1, H0546: 1, H0024: 1, T0010: 1, H0510: 1, H0428: 1, H0622: 1, H0673: 1, H0598: 1, S0036: 1, H0163: 1, H0413: 1, L0370: 1, T0041: 1, L0637: 1, L5566: 1, L0667: 1, L0772: 1, L0646: 1, L0764: 1,			



120	HLDQR62	753742	130	520 - 1005	524	Arg-122 to Ser-139, Met-144 to Glu-149.	L0794: 1, L0766: 1, L0649: 1, L0657: 1, L0788: 1, L0663: 1, S0374: 1, H0666: 1, S0330: 1, H0539: 1, H0521: 1, H0696: 1, H0478: 1, L0741: 1, L0751: 1, L0745: 1, L0747: 1, L0749: 1 and L0752: 1.			
							S0007: 10, L0748: 7, H0013: 3, S0010: 3, L0771: 3, L0438: 3, L0439: 3, L0591: 3, S0040: 2, S0222: 2, H0156: 2, H0083: 2, H0510: 2, S0003: 2, H0032: 2, L3905: 2, L0519: 2, H0521: 2, S0260: 2, L0596: 2, S0276: 2, H0265: 1, H0556: 1, S0134: 1, L3002: 1, H0675: 1, H0734: 1, S0346: 1, H0196: 1, H0309: 1, H0327: 1, H0051: 1, H0266: 1, S0314: 1, S0022: 1, H0031: 1, H0553: 1, H0212: 1, H0038: 1, H0380: 1, H0264: 1, H0100: 1, H0509: 1, S0144: 1, L0763: 1, L0372: 1,			

121	HLDQU79	740755	131	99 - 1142	525	Leu-68 to Lys-74, Tyr-109 to Lys-115, Gln-200 to Val-205, Lys-207 to Lys-214, Glu-237 to Ile-244, Ala-271 to Thr-279, Ser-317 to Ser-329, Gln-342 to Gly-348.	L0374: 1, L0803: 1, L0775: 1, L0776: 1, L0809: 1, S0216: 1, L2260: 1, L0710: 1, L2261: 1, L2654: 1, S0148: 1, L3831: 1, H0670: 1, H0539: 1, H0518: 1, H0696: 1, S0146: 1, S0406: 1, S0028: 1, L0749: 1, L0779: 1, S0026: 1, S0192: 1 and S0242: 1. L0748: 9, L0731: 7, L0771: 6, L0759: 6, H0013: 5, L0764: 4, L0747: 4, L0758: 4, H0265: 3, H0039: 3, H0038: 3, L0769: 3, L0766: 3, L0775: 3, H0144: 3, L0755: 3, S0444: 2, S0476: 2, H0318: 2, H0050: 2, L0471: 2, H0266: 2, L0374: 2, L0649: 2, L0805: 2, L0663: 2, L0664: 2, H0547: 2, S0126: 2, H0670: 2, L0740: 2, L0754: 2, L0750: 2, L0593: 2, H0667: 2, H0170: 1, H0171: 1, H0685: 1, H0662: 1, S0354: 1, S0360: 1, H0580: 1,			
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122	HLHAL68	684216	132	30 - 164	526	Leu-32 to His-38.	H0728: 1, H0151: 1, H0747: 1, L3388: 1, H0357: 1, H0586: 1, H0331: 1, H0574: 1, H0635: 1, H0575: 1, H0263: 1, H0596: 1, H0545: 1, H0012: 1, H0620: 1, H0350: 1, H0355: 1, H0510: 1, H0428: 1, H0604: 1, H0031: 1, H0553: 1, S0366: 1, H0040: 1, H0063: 1, H0059: 1, H0560: 1, H0561: 1, S0440: 1, S0422: 1, H0529: 1, L0640: 1, L0637: 1, L0761: 1, L0772: 1, L0646: 1, L4556: 1, L0774: 1, L0375: 1, L0653: 1, L0382: 1, L5622: 1, L0793: 1, L4501: 1, H0723: 1, L0352: 1, S0152: 1, S0350: 1, H0521: 1, H0696: 1, S0044: 1, H0627: 1, S0027: 1, L0749: 1, L0752: 1, H0595: 1, S0436: 1, L0591: 1, L0595: 1, L0361: 1, S0011: 1, S0194: 1, S0276: 1 and H0423: 1.	H0024: 1	
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123	HLIBD68	778073	133	186 - 338	527	Met-37 to Ser-43.	L0157: 7, L0794: 6, H0040: 4, L0439: 4, L0758: 4, H0556: 3, L0803: 3, L0005: 2, L0471: 2, H0059: 2, T0004: 2, L0769: 2, L0761: 2, L0805: 2, T0002: 1, H0685: 1, S0134: 1, S0110: 1, H0176: 1, S0356: 1, S0222: 1, H0441: 1, H0370: 1, H0486: 1, H0014: 1, H0083: 1, H0355: 1, H0286: 1, H0606: 1, H0163: 1, H0090: 1, H0561: 1, L0521: 1, L0766: 1, L0774: 1, L0809: 1, L0788: 1, L0665: 1, H0539: 1, H0696: 1, L0748: 1, L0749: 1, L0777: 1, H0543: 1 and H0423: 1.		
124	HLICQ90	791828	134	249 - 869	528	Pro-55 to Gly-66, Phe-92 to Leu-103.	H0046: 10, L0748: 6, L0758: 3, L0776: 2, L0742: 2, L0744: 2, L0750: 2, S0444: 1, S0360: 1, H0619: 1, L0717: 1, H0331: 1, H0013: 1, H0235: 1, H0355: 1, H0687: 1, H0674: 1, H0038: 1, H0623: 1, L0805: 1,		

										L0809: 1, L0789: 1, L0666: 1, L0663: 1, S0428: 1, H0520: 1, H0539: 1, S0404: 1, L0740: 1, L0749: 1, L0756: 1, S0031: 1, S0026: 1 and H0008: 1.			
125	HLQDR48	1307726	135	10 - 582	529	Arg-54 to Asn-65, Glu-80 to Ala-87, Val-170 to Arg-175, Arg-185 to Arg-190.				H0722: 2, H0574: 2, H0742: 1 and H0730: 1.			
	HLQDR48	619979	325	3 - 575	719								
126	HLTHR66	699812	136	5 - 232	530					H0036: 2, S0132: 1, S0010: 1, S0250: 1, H0591: 1 and H0130: 1.			
127	HLTIP94	1087335	137	226 - 516	531	Gly-4 to Glu-9, Asp-22 to Cys-28, Glu-39 to Leu-44, Phe-88 to Phe-94.				H0170: 1, S6026: 1 and H0591: 1.	17		
	HLTIP94	1035443	326	226 - 423	720	Gly-4 to Glu-9.							
	HLTIP94	1047690	327	3 - 899	721	Gly-1 to Glu-8, Gly-37 to Gly-61, Gln-71 to Phe-81, Asp-95 to Gly-103, Leu-126 to Ile-131, Val-166 to Glu-171.							
128	HLWAA17	629552	138	436 - 996	532	Lys-17 to Glu-27, Gln-40 to Gly-47.				S0410: 24, L0748: 18, S0436: 12, H0547: 8, L0731: 8, H0556: 7, H0039: 6, L0666: 6, H0046: 5, H0059: 5, L0775: 5, L0439: 5, L0755: 5, H0622: 4,			

					L0662: 4, L0740: 4, L0751: 4, L0779: 4, H0575: 3, H0553: 3, H0529: 3, L0769: 3, L0659: 3, L5623: 3, L0588: 3, L0593: 3, S0011: 3, H0255: 2, S0418: 2, S0442: 2, S0046: 2, H0586: 2, S0049: 2, H0424: 2, H0644: 2, H0560: 2, H0561: 2, S0002: 2, S0426: 2, L0763: 2, L0772: 2, L0646: 2, L0655: 2, L0527: 2, L0518: 2, L0783: 2, L0809: 2, L0665: 2, L0438: 2, H0519: 2, H0689: 2, H0672: 2, H0555: 2, H0631: 2, S0206: 2, L0757: 2, L0758: 2, L0485: 2, L0608: 2, L0601: 2, H0543: 2, H0171: 1, H0265: 1, S0040: 1, H0294: 1, T0049: 1, S0134: 1, H0583: 1, H0657: 1, H0484: 1, H0661: 1, H0125: 1, S0420: 1, S0354: 1, S0358: 1, S0360: 1, S0408: 1, H0580: 1, H0742: 1, S0132: 1,	
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129	HLWBK05	765310	139	280 - 1176	533	Pro-38 to Ile-45.	L0383: 1, L0663: 1, L0664: 1, S0006: 1, H0520: 1, H0593: 1, H0682: 1, H0684: 1, H0658: 1, H0670: 1, H0696: 1, S0406: 1, S0027: 1, L0754: 1, L0747: 1, L0750: 1, L0752: 1, S0434: 1, L0591: 1, L0603: 1, S0106: 1, H0668: 1, H0542: 1 and H0423: 1.  L0439: 16, L0748: 12, L0758: 9, H0013: 6, L0740: 5, L0754: 5, S0474: 4, H0265: 3, H0556: 3, H0619: 3, S0010: 3, H0266: 3, L0662: 3, L0803: 3, L0749: 3, L0752: 3, H0686: 2, S0358: 2, S0360: 2, H0632: 2, S0049: 2, H0545: 2, H0620: 2, H0594: 2, S0022: 2, H0553: 2, H0090: 2, H0100: 2, L0769: 2, L0772: 2, L0764: 2, L0794: 2, L0375: 2, L0805: 2, L0654: 2, L0776: 2, L0517: 2, L0518: 2, H0435: 2, S0406: 2, L0756: 2, L0779: 2,			
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130	HLWBY76	797609	140	432 - 1130	534			S0026: 1, S0196: 1, S0412: 1 and H0506: 1.  H0553: 7, H0412: 4, L0747: 4, L0779: 4, L0777: 4, H0615: 3, L0766: 3, H0519: 3, L0755: 3, L0591: 3, H0413: 2, L0768: 2, L0794: 2, L0754: 2, L0759: 2, L0588: 2, H0624: 1, H0716: 1, T0049: 1, S0212: 1, S0045: 1, S0278: 1, H0497: 1, L0021: 1, T0048: 1, L0471: 1, L0194: 1, H0644: 1, L0142: 1, H0269: 1, H0056: 1, H0059: 1, L0475: 1, S0422: 1, L0761: 1, L0646: 1, L0806: 1, L0655: 1, L0789: 1, L0791: 1, H0144: 1, H0726: 1, H0547: 1, H0659: 1, H0214: 1, L0780: 1, L0757: 1, L0758: 1, L0362: 1, S0026: 1, H0665: 1, H0542: 1 and H0543: 1.		
131	HLWCF05	460619	141	155 - 328	535			L0439: 9, L0766: 7, H0521: 5, L0740: 5, L0758: 5, S0010: 4, L0749: 4, H0038: 3,		



									H0375: 1, H0188: 1, S0250: 1, L0483: 1, H0598: 1, H0163: 1, H0591: 1, H0616: 1, H0623: 1, H0100: 1, H0494: 1, S0440: 1, L0598: 1, L0763: 1, L0769: 1, L0638: 1, L0800: 1, L0641: 1, L0794: 1, L0803: 1, L0775: 1, L0806: 1, L0776: 1, L0527: 1, L0659: 1, L0635: 1, L0787: 1, L0789: 1, L0666: 1, L0663: 1, L0664: 1, L0665: 1, S0428: 1, L2653: 1, L2261: 1, H0519: 1, H0435: 1, H0670: 1, H0672: 1, H0539: 1, H0696: 1, S0406: 1, H0436: 1, H0727: 1, L0755: 1, L0485: 1, H0423: 1 and H0506: 1.				
132	HL YAC95	778075	142	92 - 232	536				H0445: 1				
133	HL YAN59	1352203	143	383 - 613	537	Val-38 to Cys-45.			L0800: 2, L0021: 1, H0774: 1, L0749: 1 and H0445: 1.				
	HL YAN59	553507	328	254 - 418	722								
134	HL YAP91	553514	144	280 - 531	538				L0748: 2, L0749: 2, H0589: 1, H0039: 1, H0622: 1, H0634: 1, L0769: 1, L0800: 1,				

									L0764: 1, L0648: 1, L0794: 1, L0789: 1, H0696: 1, L0751: 1, L0747: 1, L0756: 1, L0731: 1 and H0445: 1.			
135	HLYES38	638042	145	69 - 287	539				H0687: 2 and H0445: 1.			
136	HMADK33	561941	146	161 - 619	540			Gly-43 to Gly-55.	L0438: 9, L0439: 9, L0776: 8, H0144: 7, L0741: 7, H0271: 6, S0222: 5, L0769: 5, H0052: 4, L0770: 4, L0766: 4, L0659: 4, L0666: 4, L0759: 4, H0295: 3, S0360: 3, L0370: 3, L0510: 3, H0556: 2, S0007: 2, H0261: 2, L0021: 2, H0046: 2, H0009: 2, S0051: 2, S0366: 2, H0059: 2, L0763: 2, L0784: 2, L0633: 2, L0783: 2, L0789: 2, L0790: 2, L0792: 2, L0743: 2, L0747: 2, L0749: 2, L0756: 2, L0757: 2, L0758: 2, H0445: 2, L0588: 2, L0594: 2, L0366: 2, H0265: 1, S6024: 1, H0638: 1, S0376: 1, S0045: 1, H0550: 1, H0370: 1, H0587: 1, N0009: 1, H0013: 1,			

									S0280: 1, H0599: 1, S0010: 1, S0049: 1, H0545: 1, H0457: 1, H0569: 1, H0012: 1, H0373: 1, H0051: 1, H0510: 1, H0266: 1, H0179: 1, H0416: 1, H0328: 1, S0036: 1, H0634: 1, H0087: 1, H0412: 1, L0351: 1, S0144: 1, L0638: 1, L0761: 1, L0646: 1, L0662: 1, L0767: 1, L0768: 1, L0388: 1, L0803: 1, L0774: 1, L0775: 1, L0375: 1, L0651: 1, L0806: 1, L0515: 1, L0809: 1, S0428: 1, S0216: 1, H0699: 1, H0693: 1, H0684: 1, H0648: 1, H0710: 1, H0521: 1, H0696: 1, H0187: 1, H0436: 1, S0028: 1, L0750: 1, L0779: 1, L0731: 1, S0260: 1, H0595: 1, L0599: 1, S0192: 1, S0276: 1, H0542: 1 and H0352: 1.					
137	HMADS41	596831	147	267 - 533	541				L0794: 4, L0375: 3, H0575: 2, L0800: 2, L0789: 2, H0556: 1, H0662: 1, S0418: 1,					

138	HMAMI15	1352406	148	4 - 1023	542	Gly-33 to Lys-41, Pro-52 to Lys-60, Asn-81 to Ala-86, Lys-156 to Met-164, Gln-283 to Lys-292, Glu-303 to Gly-308.	H0619: 1, H0549: 1, H0590: 1, H0052: 1, H0083: 1, H0266: 1, H0286: 1, H0644: 1, S0036: 1, H0433: 1, H0412: 1, H0413: 1, T0042: 1, S0144: 1, S0142: 1, S0344: 1, L0770: 1, L0761: 1, L0774: 1, H0518: 1, L0777: 1, L0758: 1 and H0665: 1.		
	HMAMI15	1049263	329	3 - 923	723	Gly-33 to Lys-41, Pro-52 to Lys-60, Asn-81 to Ala-86.	H0624: 2, S0354: 2, S0442: 1, S0444: 1, S0278: 1, S0222: 1, H0586: 1, L0021: 1, H0036: 1, H0031: 1, L0769: 1, L0804: 1, L0774: 1, H0658: 1, H0521: 1, S0406: 1, L0748: 1 and S0462: 1.		
139	HMCIFY13	635301	149	175 - 369	543		L0800: 2, H0550: 1, H0497: 1, S0344: 1, L0769: 1, L0789: 1 and L0749: 1.		
140	HMDAB56	560676	150	273 - 407	544		L0809: 2, H0346: 1, H0271: 1, L0774: 1 and L0532: 1.		
141	HMEED18	560775	151	34 - 699	545	Gln-85 to Lys-91, Pro-106 to Ser-117,	L0439: 20, L0157: 8, L0794: 8, L0805: 6,		





									L2653: 1, H0144: 1, H0659: 1, H0658: 1, H0670: 1, S0378: 1, H0696: 1, H0555: 1, H0576: 1, S0028: 1, L0745: 1, L0747: 1, L0780: 1, S0434: 1, S0436: 1 and H0668: 1.			
142	HMEFT54	520307	152	332 - 451	546				L0757: 3, L0662: 2, H0686: 1, S0444: 1, H0266: 1, L0055: 1, L0763: 1, L0800: 1, L0764: 1, L0768: 1, L0805: 1, L0653: 1, L0666: 1, H0690: 1, H0672: 1, L0751: 1, L0777: 1 and L0758: 1.			
143	HMEGF92	520304	153	92 - 280	547	Ser-34 to Ser-39.			H0266: 1, L0438: 1 and L0439: 1.			
144	HMSDL37	973996	154	531 - 725	548	Ser-31 to Lys-45, Pro-47 to Pro-53, Ser-58 to Arg-63.			L0517: 2, S0050: 1, H0014: 1, H0510: 1, H0040: 1, H0264: 1, S0002: 1, S0374: 1 and L0758: 1.	3,3p		
	HMSDL37	895429	330	528 - 722	724	Ser-31 to Lys-45, Pro-47 to Pro-53, Ser-58 to Arg-63.						
	HMSDL37	904241	331	565 - 645	725							
	HMSDL37	750927	332	2 - 151	726							
145	HMSFI26	560229	155	120 - 308	549				S0002: 1			
146	HMSJU68	427121	156	272 - 421	550	Met-1 to Gly-7.			L0560: 5, L0545: 4, S0002: 2, L5574: 2,			

147	HMTBI36	1301451	157	256 - 3129	551	<p>Thr-25 to Lys-31,  Leu-116 to Glu-121,  Asp-153 to Thr-161,  Gly-164 to Arg-170,  Ser-216 to Gly-226,  Pro-229 to Gln-237,  Arg-246 to Glu-260,  Arg-291 to Gln-298,  Arg-341 to Glu-348,  Lys-356 to Ser-364,  Gln-387 to Phe-398,  Leu-429 to Phe-435,  Trp-455 to Ile-463,  Tyr-489 to Ala-496,  Thr-518 to Ala-525,  Lys-542 to Leu-549,  Pro-627 to Ile-632,  Ser-637 to Arg-651,  Ser-821 to Gly-827,  Gln-921 to Ser-927,  Arg-932 to Ile-941,  Ser-945 to Arg-957.</p>	<p>H0240: 1, S0046: 1,  H0333: 1, H0597: 1,  H0014: 1, L5569: 1,  L0533: 1, L0519: 1,  L0544: 1, S0374: 1,  H0520: 1, S0454: 1,  S0406: 1 and L3813: 1.  L0794: 25, L0766: 14,  H0457: 10, L0809: 8,  L0761: 7, L0659: 7,  L0764: 6, L0803: 6,  H0255: 4, H0624: 3,  H0747: 3, H0592: 3,  H0581: 3, L0768: 3,  L0787: 3, L0789: 3,  L0747: 3, S0045: 2,  H0749: 2, L0717: 2,  H0617: 2, L0648: 2,  L0806: 2, L0783: 2,  L0666: 2, H0703: 2,  L0743: 2, L0750: 2,  L0779: 2, H0657: 1,  L0785: 1, H0661: 1,  H0402: 1, S0420: 1,  S0354: 1, H0580: 1,  S0222: 1, H0600: 1,  H0586: 1, H0587: 1,  H0559: 1, H0069: 1,  H0318: 1, S0474: 1,  H0421: 1, H0439: 1,  H0009: 1, H0123: 1,  H0266: 1, H0271: 1,  H0634: 1, H0264: 1,</p>		
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148	HIMVBS81	639203	158	34 - 453	552	Gln-921 to Ser-927, Arg-932 to Ile-941, Ser-945 to Arg-957.	H0544: 4, L0775: 3, L0748: 3, H0265: 2, H0046: 2, T0010: 2, H0424: 2, L0769: 2, L0771: 2, L0774: 2, L0659: 2, L0382: 2, H0696: 2, L0750: 2, L0755: 2, L0731: 2, L0757: 2, L0758: 2, L0608: 2, H0685: 1, S0040: 1, S0114: 1, S0218: 1, L0785: 1, H0341: 1, S0212: 1, H0484: 1, H0662: 1, S0360: 1, H0411: 1, H0592: 1, L0623: 1, H0156: 1, H0253: 1, H0263: 1, H0204: 1, H0150: 1, H0050: 1, H0012: 1, H0510: 1, H0606: 1, L0055: 1, S0364: 1, H0124: 1, H0163: 1, H0090: 1, H0087: 1, H0413: 1, H0494: 1, H0509: 1, S0210: 1, L0770: 1, L0764: 1, L0773: 1, L0794: 1, L0766: 1, L0658: 1, L0666: 1, S0126: 1, S3012: 1,		
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									S3014: 1, L0745: 1, L0747: 1, L0777: 1, S0031: 1, S0434: 1, L0605: 1, L0366: 1 and H0543: 1.			
149	HMWDC28	460487	159	124 - 252	553				H0341: 2, L0803: 2, L0439: 2, L0747: 2, S0376: 1, S0360: 1, S0222: 1, H0674: 1, H0038: 1, L0655: 1, L0809: 1, L0666: 1, L0754: 1, L0756: 1, L0757: 1 and L0591: 1.			
150	HMWFT65	562063	160	72 - 437	554				H0341: 1			
151	HNEEE24	553558	161	213 - 428	555				L0747: 2, L0758: 2, H0580: 1 and H0179: 1.			
152	HNFFC43	753337	162	488 - 691	556		Asp-21 to Ser-29.		H0521: 6, H0036: 2, H0052: 2, H0271: 2, H0551: 2, H0543: 2, H0265: 1, H0556: 1, S0354: 1, H0392: 1, H0581: 1, H0063: 1, H0059: 1, H0494: 1, H0561: 1, L3829: 1, H0520: 1, H0522: 1, S0436: 1, L0595: 1, H0506: 1 and L0600: 1.			
153	HNFGF20	768395	163	206 - 637	557		Pro-97 to Asp-104.		H0556: 2, H0271: 2 and H0619: 1.			
154	HNFIY77	634551	164	228 - 929	558		Pro-47 to Met-53, Ser-130 to Ser-138.		L0539: 1, S0442: 1, H0619: 1, H0581: 1, T0010: 1, H0416: 1, H0622: 1, H0131: 1,			

155	HNFJF07	577013	165	86 - 286	559	Val-25 to Gly-33.	H0521: 1 and H0653: 1. H0271: 2, H0581: 1, H0051: 1, H0163: 1, L0599: 1 and H0422: 1. S0052: 1		
156	HNGDJ72	532619	166	185 - 523	560	Asp-15 to Tyr-21, Pro-29 to Asn-39.	S0052: 1		
157	HNGEP09	499076	167	72 - 320	561	Asp-45 to Thr-50.	S0052: 2		
158	HNGFR31	553552	168	108 - 380	562		S0052: 1		
159	HNGIJ31	519120	169	135 - 245	563	Pro-18 to Glu-25.			
160	HNGJE50	561568	170	77 - 217	564		S0052: 1		
161	HNGND37	839224	171	388 - 636	565	Asn-46 to Ser-54.	L0749: 4, L0439: 3, H0100: 2, L0770: 2, L0776: 2, H0556: 1, H0638: 1, H0441: 1, T0010: 1, H0687: 1, L0055: 1, L0769: 1, L0809: 1, S0428: 1, H0522: 1, H0694: 1, L0758: 1, L0589: 1 and L0592: 1.		
162	HNGOI12	1041375	172	27 - 200	566	Met-1 to Gly-9.	S0428: 1	11	
	HNGOI12	838184	334	27 - 200	728	Met-1 to Gly-9.			
	HNGOI12	839283	335	596 - 877	729				
163	HNEHU93	634851	173	57 - 302	567		S0053: 1		
164	HNHFM14	664507	174	38 - 280	568	Glu-67 to Ala-74.	L0747: 5, H0619: 4, S0406: 4, L0439: 4, L0777: 4, H0617: 2, L0770: 2, L0769: 2, L0803: 2, L0438: 2, L3827: 2, S0328: 2, L0749: 2, L0779: 2, H0265: 1, L3643: 1,	1	

									H0484: 1, S0418: 1, H0747: 1, L3388: 1, H0618: 1, S0010: 1, H0052: 1, H0570: 1, H0012: 1, H0014: 1, H0510: 1, H0288: 1, H0622: 1, S0366: 1, H0040: 1, H0623: 1, L0351: 1, T0042: 1, L0761: 1, L0764: 1, L0767: 1, L0805: 1, L0655: 1, L0809: 1, S0053: 1, L3828: 1, H0520: 1, H0435: 1, H0659: 1, S3014: 1, L0743: 1, L0756: 1, L0758: 1 and H0136: 1.			
165	HNHFR04	646709	175	71 - 307	569				S0053: 2 and S0428: 1.			
166	HNHNB29	895462	176	40 - 201	570	Glu-17 to Lys-30, Val-43 to Asn-53.			S0216: 1			
167	HNHOD46	843488	177	12 - 251	571				S0216: 1			
168	HNTBI26	1310821	178	28 - 990	572	Pro-56 to Pro-63, Met-92 to Thr-98, Ser-112 to Pro-120, Pro-162 to Glu-173, Ala-200 to Ser-210, Lys-311 to Asn-320.			H0124: 23, L0774: 4, L0740: 3, S0212: 2, S0360: 2, L3388: 2, L0659: 2, L0757: 2, S0436: 2, H0170: 1, H0713: 1, H0580: 1, S0045: 1, H0393: 1, S0220: 1, H0333: 1, H0643: 1, H0574: 1, H0013: 1, S0280: 1, H0581: 1, H0544: 1, H0150: 1, H0059: 1,			

									H0509: 1, L0369: 1, L0640: 1, L0521: 1, L0363: 1, L0775: 1, L0654: 1, L0776: 1, L0559: 1, L0384: 1, L0790: 1, L0664: 1, L2258: 1, L2260: 1, H0519: 1, S0027: 1, S0206: 1, L0747: 1, L0749: 1, L0780: 1, L0731: 1, L0759: 1 and H0542: 1.			
	HNTBI26	796807	336	32 - 547	730	Pro-56 to Pro-63, Met-92 to Thr-98, Ser-112 to Pro-120, Pro-162 to Ser-169.						
	HNTBI26	590738	337	16 - 411	731	Pro-56 to Pro-63, Met-92 to Thr-98, Arg-107 to Pro-120.						
169	HNTBL27	545534	179	100 - 447	573	Arg-45 to Thr-52, Tyr-60 to Gly-66, Ala-87 to Trp-92, Leu-105 to Ser-115.	L0794: 3, L0663: 2, S0360: 1, H0042: 1, H0253: 1, H0150: 1, H0633: 1, S0142: 1, H0538: 1, L0804: 1, L0790: 1, L0791: 1, L0666: 1, L0664: 1, L0665: 1, H0519: 1, L0747: 1, L0749: 1, L0779: 1, L0777: 1, L0755: 1 and L0731: 1.					
170	HNTCE26	1160395	180	111 - 1316	574	Tyr-2 to Gly-15, Trp-192 to Asp-199, Lys-248 to Leu-253,	H0580: 5, L0754: 5, H0615: 4, L0805: 4, L0748: 4, L0731: 4,					



						Arg-330 to Lys-336, Gln-354 to Val-364, Val-383 to Ser-392.	H0031: 3, S0440: 3, L0659: 3, L0758: 3, L2346: 2, S0278: 2, L0804: 2, L0809: 2, H0547: 2, H0352: 2, H0657: 1, H0656: 1, S0418: 1, S0442: 1, S0444: 1, L3649: 1, H0741: 1, H0645: 1, H0574: 1, H0486: 1, L3521: 1, H0013: 1, S0010: 1, H0327: 1, H0046: 1, L0041: 1, H0510: 1, S0214: 1, H0328: 1, H0030: 1, H0553: 1, H0644: 1, H0032: 1, S0344: 1, S0002: 1, L0369: 1, L0667: 1, L0364: 1, L0794: 1, L0803: 1, L0775: 1, L0776: 1, L0789: 1, L0666: 1, L0663: 1, L2653: 1, L0438: 1, H0519: 1, H0670: 1, H0521: 1, L0744: 1, L0439: 1, L0747: 1, L0779: 1, L0591: 1 and L3374: 1.			
	HNTCE26	853373	338	57 - 422	732	Arg-75 to Lys-81, Gln-99 to Asp-109.				
171	HNTNC20	700627	181	270 - 926	575	Gln-23 to Gly-30, Gln-35 to Gln-43, Leu-73 to Glu-84,	L0803: 2, L0731: 2, H0580: 1, H0587: 1, S0005: 1, L0369: 1,			

172	HNTNI01	1352285	182	307 - 534	576	Arg-125 to Pro-133, Ser-140 to Thr-145, Thr-153 to Thr-164. Lys-71 to Trp-76.	L0647: 1, L0666: 1, H0144: 1, H0520: 1, S0152: 1 and L0759: 1. L0747: 5, H0545: 3, H0520: 3, L0439: 3, L0803: 2, L0790: 2, H0547: 2, L0740: 2, L0751: 2, L0779: 2, L0759: 2, L0593: 2, H0170: 1, S0005: 1, H0485: 1, H0013: 1, L0564: 1, L0770: 1, L0794: 1, L0809: 1, H0519: 1, S0378: 1, L0756: 1, L0777: 1 and H0667: 1.		
	HNTNI01	699848	339	306 - 455	733				
173	HNTSY18	1041383	183	257 - 526	577	Pro-53 to Arg-59, Ala-64 to Cys-69.	L0805: 2, H0619: 1, H0547: 1 and S0190: 1.	7	
	HNTSY18	897950	340	420 - 656	734	Pro-13 to Ser-19, Glu-25 to Glu-31, Pro-44 to Gly-53, Gly-74 to Arg-79.			
174	HOCNF19	835049	184	166 - 429	578	Thr-45 to Pro-56, Ser-66 to Lys-74.	S0442: 2		
175	HODDF13	684307	185	46 - 171	579	Thr-28 to Ser-40.	H0328: 1		
176	HODDN92	422913	186	434 - 541	580		L0758: 14, H0457: 10, H0556: 5, S0114: 5, L0748: 5, L0756: 5, H0657: 4, H0620: 4, H0328: 4, H0591: 4, L0754: 4, L0779: 4, H0589: 3, L0532: 3,		



									S0434: 1, S0011: 1, S0026: 1, H0543: 1 and H0423: 1.			
177	HODEJ32	835027	187	358 - 489	581				H0615: 1			
178	HOFMQ33	1184465	188	49 - 1503	582			Leu-37 to Gly-44, Thr-137 to Leu-144, Ala-178 to Asn-184, Asp-194 to Val-201, Leu-252 to Glu-258, Asp-280 to Tyr-293, Asn-296 to Thr-301, Asp-322 to Asp-348, Asn-363 to Ser-368, His-370 to Thr-378, Asn-380 to Cys-386, Glu-391 to Cys-399, Leu-421 to Arg-426, Glu-454 to Tyr-459.	H0415: 1			
	HOFMQ33	919896	341	48 - 1502	735			Leu-37 to Gly-44, Pro-46 to Gly-51, Thr-137 to Leu-144, Ala-178 to Asn-184, Asp-194 to Val-201, Leu-252 to Glu-258, Asp-280 to Tyr-293, Asn-296 to Thr-301, Asp-322 to Asp-348, Asn-363 to Ser-368, His-370 to Thr-378, Asn-380 to Cys-386, Glu-391 to Cys-399, Leu-421 to Arg-426, Glu-454 to Tyr-459.				

	HOFMQ33	906694	342	78 - 875	736	Leu-37 to Gly-43.			
	HOFMQ33	902639	343	724 - 741	737				
	HOFMQ33	702186	344	123 - 374	738	Met-2 to Ser-9.			
179	HOHBY44	873264	189	170 - 724	583	Glu-23 to Gln-30, Asn-42 to Gly-65, Thr-84 to Lys-100, Glu-105 to Ser-110, Arg-132 to Phe-138, Pro-159 to Arg-172.	L0564: 9, S0250: 5, S0126: 3, L0740: 3, L0757: 3, S0360: 2, H0551: 2, H0171: 1, S0376: 1, H0489: 1, L0717: 1, T0039: 1, H0013: 1, L0021: 1, H0327: 1, H0545: 1, H0014: 1, S0336: 1, S0003: 1, H0622: 1, H0031: 1, L0520: 1, L0372: 1, L0764: 1, L0771: 1, L0773: 1, S0380: 1, S0350: 1 and S0026: 1.	15	
	HOHBY44	873263	345	2 - 232	739	Cys-25 to Asn-36.			
	HOHBY44	785886	346	54 - 305	740	Ser-30 to Met-36, Ile-38 to Pro-46, Gln-78 to Gly-88, Thr-98 to Pro-105, Gly-110 to Ser-122, Ser-136 to Trp-144.			
180	HOQBJ82	1352356	190	361 - 852	584		L0766: 12, L0758: 7, H0616: 4, L0439: 4, L0754: 4, L0747: 4, L0779: 4, L0777: 4, L0601: 4, H0657: 3, H0656: 3, H0081: 3, H0031: 3, H0038: 3, S0222: 2, H0455: 2, H0618: 2, H0617: 2, T0042: 2, H0494: 2, S0210: 2, H0529: 2, L0769: 2, L0662: 2, L0794: 2, L0665: 2,		

					H0445: 2, H0543: 2, H0170: 1, H0394: 1, H0556: 1, T0002: 1, S0029: 1, H0662: 1, S0358: 1, S0045: 1, S0046: 1, S0140: 1, L0717: 1, H0370: 1, H0392: 1, H0497: 1, H0574: 1, H0253: 1, H0318: 1, H0597: 1, H0544: 1, H0545: 1, H0178: 1, L0157: 1, L0471: 1, S0050: 1, H0014: 1, H0051: 1, T0010: 1, H0408: 1, H0266: 1, H0188: 1, H0290: 1, S0022: 1, H0135: 1, H0090: 1, H0040: 1, H0634: 1, H0264: 1, S0448: 1, H0641: 1, S0142: 1, S0344: 1, L0770: 1, L0637: 1, L0645: 1, L0771: 1, L0521: 1, L0768: 1, L0803: 1, L0806: 1, L0805: 1, L0652: 1, L0653: 1, L0776: 1, L0655: 1, L0629: 1, L0659: 1, L0789: 1, L0791: 1, L0663: 1, L0664: 1, H0519: 1, H0682: 1, H0539: 1, H0521: 1,
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									H0522: 1, H0134: 1, H0214: 1, L0749: 1, L0750: 1, H0667: 1, H0542: 1, H0423: 1 and H0422: 1.			
	HOQBJ82	858338	347	102 - 584	741	Ser-30 to Met-36, Ile-38 to Pro-46, Gln-78 to Gly-88, Thr-98 to Pro-105, Gly-110 to Ser-122.						
	HOQBJ82	857453	348	55 - 1029	742							
181	HOSBY40	589431	191	89 - 259	585				S0418: 1, H0393: 1, S0003: 1, L0766: 1, L0804: 1 and S0052: 1.			
182	HOSDJ25	854234	192	1076 - 1195	586	Gly-18 to Lys-23, Pro-31 to Gly-38.			L0754: 4, L0749: 4, L0659: 3, L0755: 3, S0356: 2, L0803: 2, L0750: 2, L0779: 2, L0599: 2, S0029: 1, H0661: 1, S0354: 1, H0642: 1, T0040: 1, L0021: 1, H0599: 1, H0510: 1, S0003: 1, H0674: 1, H0316: 1, H0623: 1, S0422: 1, L0794: 1, L0522: 1, L0774: 1, L0526: 1, L0809: 1, H0520: 1, H0659: 1, H0670: 1, L0752: 1, L0608: 1 and S0242: 1.			
	HOSDJ25	566845	349	146 - 268	743	Gly-18 to Lys-23, Pro-31 to Gly-38.						

183	HOUQC17	429229	193	508 - 3408	587	Gly-8 to Leu-14, Met-18 to Phe-30.	L0731: 19, S0414: 18, L0665: 18, L0747: 10, L0749: 9, H0411: 7, H0431: 7, L0662: 7, L0750: 6, H0031: 5, L0748: 5, L0439: 5, S0194: 4, H0717: 3, H0014: 3, L0666: 3, L0663: 3, S0126: 3, H0690: 3, L0740: 3, L0752: 3, L0599: 3, L0361: 3, H0713: 2, S0212: 2, H0427: 2, S0280: 2, H0544: 2, S0003: 2, H0644: 2, L0598: 2, L0649: 2, L0803: 2, L0657: 2, L0659: 2, L0809: 2, L3872: 2, L0789: 2, L0438: 2, S0406: 2, H0478: 2, L0744: 2, L0754: 2, L0756: 2, L0779: 2, L0757: 2, L0758: 2, H0667: 2, S0276: 2, H0739: 1, H0624: 1, H0170: 1, H0171: 1, S0040: 1, H0295: 1, L3403: 1, S0354: 1, S0358: 1, S0444: 1, S0360: 1, S0408: 1, L1441: 1, H0730: 1, H0734: 1, S6022: 1, H0587: 1,		
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									H0486: 1, T0039: 1, L3506: 1, L3530: 1, H0599: 1, H0036: 1, S0010: 1, H0545: 1, L0471: 1, L0163: 1, H0687: 1, S0250: 1, L0483: 1, H0030: 1, H0553: 1, L0142: 1, H0617: 1, H0616: 1, T0067: 1, H0380: 1, H0100: 1, H0494: 1, S0210: 1, UNKWN: 1, L0769: 1, L3904: 1, L5565: 1, L0643: 1, L0767: 1, L0774: 1, L0775: 1, L0375: 1, L0784: 1, L0776: 1, L0656: 1, L4669: 1, L0783: 1, L0384: 1, L5622: 1, L2259: 1, H0693: 1, H0724: 1, H0520: 1, H0670: 1, H0648: 1, H0672: 1, S0044: 1, L0777: 1, L0755: 1, L0759: 1, S0031: 1, S0260: 1, S0192: 1, S0242: 1 and S0196: 1.				
184	HPEAD79	520202	194	51 - 176	588	Lys-16 to Ser-21, Gly-36 to Asp-41.	H0165: 1						
185	HPIBO15	1310868	195	128 - 763	589	Asp-40 to Glu-50, Ser-59 to Gly-69, Leu-109 to Lys-117,	L0747: 8, L0749: 5, L0755: 5, H0013: 3, L0769: 3, L0731: 3,						



	HPJCL22	1046434	355	232 - 666	749	Thr-43 to Asp-59, Gly-88 to Gly-94, Lys-105 to Ile-115. Ala-55 to Asn-60, Lys-65 to Met-71, Leu-75 to Asn-86, Asp-93 to Asp-110, Leu-130 to Cys-138, Gln-149 to Glu-154, Thr-172 to Ile-179, Glu-185 to Arg-192.				
189	HPMDK28	846357	199	64 - 669	593		<p>S0358: 5, L0809: 4, L0742: 4, L0743: 4, L0590: 4, H0543: 4, S0360: 3, H0031: 3, S0422: 3, L0763: 3, L0764: 3, L0766: 3, L0754: 3, H0716: 2, H0333: 2, H0266: 2, H0617: 2, L4497: 2, L0769: 2, L0776: 2, H0658: 2, H0696: 2, L0748: 2, L0749: 2, H0445: 2, S0434: 2, S0110: 1, H0663: 1, L0481: 1, H0730: 1, H0747: 1, H0411: 1, H0431: 1, H0370: 1, H0574: 1, H0632: 1, L2490: 1, H0253: 1, H0052: 1, H0546: 1, H0545: 1, H0150: 1, H0123: 1, H0012: 1, S0050: 1, S0051: 1, H0188: 1, S0003: 1, H0428: 1, T0006: 1, H0606: 1, H0673: 1, H0090: 1, H0040: 1, H0412: 1, T0069: 1, S0112: 1, S0344: 1, H0538: 1, H0529: 1,</p>			

									L0770: 1, L0761: 1, L0662: 1, L0768: 1, L0794: 1, L0560: 1, L0775: 1, L0806: 1, L0517: 1, L0540: 1, L0384: 1, L5622: 1, L0666: 1, L0665: 1, L2260: 1, L2654: 1, S0374: 1, H0684: 1, L3832: 1, S0004: 1, S0390: 1, S3014: 1, L0439: 1, L0740: 1, L0747: 1, L0756: 1, L0779: 1, S0436: 1, L0480: 1, L0596: 1, S0026: 1, S0276: 1, S0196: 1, L2854: 1 and L3612: 1.			
	HPMDK28	639118	356	58 - 663	750	Ala-55 to Asn-60, Lys-65 to Met-71, Leu-75 to Asn-86, Asp-93 to Asp-110, Leu-130 to Cys-138, Gln-149 to Glu-154, Thr-172 to Ile-179, Glu-185 to Arg-192.						
190	HPRAL78	1352342	200	62 - 1321	594	Pro-31 to Thr-48, Arg-62 to Gly-70, Ala-74 to Glu-87, Lys-123 to Asp-129, Pro-162 to Gly-167, Glu-170 to Gly-189, Arg-220 to Asn-228,	H0694: 5, L0759: 5, L0766: 4, H0261: 3, S0222: 3, H0486: 3, H0052: 3, L0731: 3, L3316: 2, H0252: 2, L0764: 2, L0662: 2, L0775: 2, L0657: 2,	3				



									L0605: 1, L0599: 1 and L3352: 1.			
	HPRAL78	844216	357	70 - 1245	751	Pro-31 to Thr-48, Arg-62 to Gly-70, Ala-74 to Glu-87, Lys-123 to Asp-129, Pro-162 to Gly-167, Glu-170 to Gly-189, Arg-220 to Asn-228.						
	HPRAL78	484735	358	148 - 339	752	Ser-49 to Arg-54.						
191	HRABA80	882176	201	144 - 452	595	Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87.			H0555: 1			
	HRABA80	588460	359	130 - 438	753	Ala-30 to Gly-36, Asp-45 to Trp-50, Lys-65 to Cys-71, Pro-80 to Cys-87.						
192	HRACD15	871221	202	252 - 410	596				H0556: 15, H0265: 8, L0751: 8, H0617: 7, L0662: 7, L0766: 5, L0809: 5, H0040: 4, H0494: 4, S0142: 4, L0769: 4, H0555: 4, L0750: 4, H0543: 4, H0341: 3, L0534: 3, H0486: 3, L0649: 3, L0666: 3, H0658: 3, L0749: 3, L0758: 3, H0624: 2, S0040: 2, L0415: 2, H0261: 2, H0549: 2, H0550: 2, H0618: 2, H0052: 2,			



									S0422: 1, L0598: 1, H0529: 1, L0763: 1, L0638: 1, L4747: 1, L0761: 1, L0800: 1, L0648: 1, L0774: 1, L0651: 1, L0378: 1, L0776: 1, L0629: 1, L0382: 1, L0788: 1, L0791: 1, L0663: 1, H0144: 1, H0593: 1, H0689: 1, H0659: 1, S0406: 1, S0037: 1, L0745: 1, L0779: 1, L0752: 1, L0755: 1, S0394: 1, L0593: 1, S0026: 1, H0665: 1, H0542: 1, H0423: 1 and H0506: 1.					
	HRACD15	706332	360	252 - 413	754									
193	HRACJ35	877666	203	132 - 1550	597	Arg-31 to Lys-37, Lys-58 to Glu-65, Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282.	L0731: 11, L0803: 7, L0748: 7, L0517: 6, L0809: 6, L0749: 6, L0439: 5, S0410: 4, S0002: 4, L0770: 4, L0794: 4, L0805: 4, L3212: 4, S0436: 4, L3388: 3, H0553: 3, L0506: 3, L0747: 3, L0752: 3, H0713: 2, H0661: 2, H0244: 2, H0156: 2, H0644: 2, L0662: 2, L0775: 2, L0666: 2, L0438: 2,							





							Asp-157 to Gly-168, Ile-219 to Gly-225, Ala-260 to Ser-268, Thr-276 to Glu-282.				
	HRACJ35	470546	362	1 - 534	756		Ile-9 to Gly-15, Ala-50 to Ser-58, Thr-66 to Glu-72.				
194	HRGBL78	910133	204	30 - 1109	598		Thr-48 to Arg-56, Pro-122 to Glu-127, Lys-135 to Cys-143, Ala-180 to Gly-185, Ala-230 to Tyr-238, Thr-244 to Gln-255, Pro-274 to Ser-279, Thr-284 to Phe-306, Leu-345 to Thr-354.	L0740: 25, L0766: 5, L0655: 4, H0650: 2, H0657: 2, H0656: 2, H0402: 2, H0581: 2, L0761: 2, L0794: 2, H0306: 1, S0408: 1, H0318: 1, H0046: 1, H0266: 1, S0038: 1, H0429: 1, H0560: 1, S0344: 1, L0789: 1, S0053: 1, H0689: 1, H0134: 1, L0779: 1, L0777: 1 and H0445: 1.	1		
	HRGBL78	904040	363	30 - 626	757		Thr-48 to Arg-56, Pro-122 to Glu-127, Ala-136 to Tyr-141.				
	HRGBL78	904621	364	11 - 19	758						
	HRGBL78	863802	365	1048 - 1146	759		Pro-24 to Arg-32.				
195	HROAJ39	1181699	205	10 - 1146	599		Ile-4 to Tyr-10, Arg-119 to Pro-126, Glu-152 to Gly-158, Thr-209 to Phe-215.	H0316: 1, L3905: 1, L0565: 1, L0438: 1, H0521: 1, L0439: 1 and L0594: 1.			
	HROAJ39	1114849	366	31 - 879	760		Arg-40 to Pro-47, Glu-73 to Gly-79, Thr-130 to Phe-136, Lys-277 to Lys-283.				

	HROAJ39	1027712	367	247 - 1104	761	Arg-40 to Pro-47, Glu-73 to Gly-79, Thr-130 to Phe-136.			
196	HROBD68	827306	206	122 - 268	600	Thr-19 to Thr-25.	L0509: 9, L0766: 4, L0515: 2, L0783: 2, S0342: 1, S0114: 1, S0218: 1, H0589: 1, H0645: 1, H0592: 1, H0250: 1, H0581: 1, H0057: 1, H0252: 1, H0328: 1, H0674: 1, H0598: 1, H0090: 1, H0634: 1, H0488: 1, H0625: 1, S0426: 1, L0506: 1, L0667: 1, L0499: 1, L0803: 1, L0493: 1, L0514: 1, L0511: 1, L0809: 1, S0052: 1, S0428: 1, H0683: 1, S0152: 1, S0136: 1, L0748: 1, L0751: 1, L0759: 1, L0599: 1 and H0543: 1.		
197	HSAWD74	460527	207	142 - 570	601	Leu-51 to Gly-77, Ile-117 to Pro-125.	H0068: 3, S0114: 2, L0534: 2, L0740: 2, H0717: 1, S0134: 1, S0442: 1, S0354: 1, S0476: 1, H0333: 1, H0009: 1, H0560: 1, L5565: 1 and H0576: 1.	7	
	HSAWD74	371416	368	122 - 256	762	Thr-25 to Cys-30, Pro-35 to Arg-42.			
198	HSDEK49	1352253	208	60 - 1256	602	Val-29 to Val-37,	H0031: 7, L0439: 7,		

					Asp-71 to His-76, Gln-78 to Gly-84, Met-105 to His-110, Trp-117 to Asn-123, Lys-179 to Pro-187, Gly-218 to Asp-224, Leu-237 to Ala-243, Thr-256 to Asp-268, Ser-275 to Lys-280, Arg-308 to Glu-314, Glu-326 to Glu-332, Cys-343 to Asp-359.	L0754: 7, L3388: 6, L0731: 6, S0002: 5, H0580: 4, H0575: 3, H0309: 3, L0438: 3, H0555: 3, L0758: 3, S0360: 2, L3649: 2, H0553: 2, S0344: 2, S0426: 2, L0775: 2, S0330: 2, L0747: 2, L0779: 2, S0260: 2, L0599: 2, L0603: 2, H0739: 1, H0170: 1, S0116: 1, S0354: 1, S0444: 1, L3645: 1, H0270: 1, S0280: 1, H0590: 1, H0581: 1, H0251: 1, H0014: 1, H0355: 1, H0030: 1, H0644: 1, H0674: 1, H0090: 1, H0063: 1, S0142: 1, L0770: 1, L0769: 1, L0651: 1, L0776: 1, L0659: 1, L0519: 1, L0664: 1, H0682: 1, L0749: 1, L0752: 1, S0031: 1 and H0506: 1.		
HSDEK49	625998	369	126 - 1043	763	Val-29 to Val-37, Asp-71 to His-76, Gln-78 to Gly-84, Met-105 to His-110, Trp-117 to Gly-122, Gln-136 to Lys-141,			

199	HSDFJ26	834619	209	99 - 767	603	<p>Leu-143 to Ala-149, Thr-162 to Asp-174, Ser-181 to Lys-186, Arg-214 to Glu-220, Glu-232 to Glu-238, Cys-249 to Asp-265.</p> <p>Ala-21 to Glu-31, Thr-37 to Cys-43, Asp-62 to Ser-79, Lys-134 to Gly-146, Leu-164 to Met-169, Glu-171 to Lys-201.</p>	<p>S0026: 6, S0360: 4, L0662: 4, L0747: 4, L0759: 4, L0755: 3, S0408: 2, H0575: 2, S0474: 2, H0251: 2, H0673: 2, L0766: 2, L0804: 2, L0665: 2, L0608: 2, H0543: 2, H0171: 1, H0686: 1, H0613: 1, H0427: 1, L0021: 1, T0082: 1, H0309: 1, H0150: 1, H0024: 1, L0163: 1, H0266: 1, H0271: 1, S0338: 1, H0252: 1, H0615: 1, H0428: 1, H0030: 1, H0040: 1, H0647: 1, L0369: 1, L0500: 1, L0769: 1, L0638: 1, L0637: 1, L0764: 1, L0767: 1, L0768: 1, L0364: 1, L0794: 1, L0649: 1, L0775: 1, L0805: 1, L0659: 1, L0382: 1, L0666: 1, S0052: 1, H0697: 1, S0328: 1,</p>		
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									S0330: 1, S0380: 1, H0521: 1, S0406: 1, H0478: 1, L0754: 1, L0745: 1, L0749: 1, L0779: 1, L0780: 1, L0752: 1, S0031: 1, L0601: 1, S0242: 1 and H0542: 1.			
	HSDFJ26	836071	370	99 - 317	764			Ala-21 to Glu-31, Thr-37 to Cys-43, Pro-64 to Asp-69.				
200	HSDJA15	795252	210	247 - 705	604			Thr-32 to Lys-40, Lys-146 to Glu-152.				
201	HSDJM31	491112	211	351 - 473	605				S0360: 1, L0794: 1, L0759: 1 and S0260: 1.			
202	HSDSB09	1301498	212	16 - 423	606			Glu-33 to Glu-56, Thr-75 to Cys-81.	L0803: 14, L0774: 4, L0770: 2, H0409: 1, H0331: 1 and H0555: 1.			
	HSDSB09	463645	371	22 - 387	765			Glu-33 to Glu-56, Thr-75 to Cys-81.				
203	HSHAX21	612823	213	177 - 392	607			Leu-23 to Met-30.	L0754: 6, S0422: 4, L0803: 4, L0766: 3, L0659: 3, H0638: 2, S0442: 2, S0360: 2, H0392: 2, L0794: 2, L0649: 2, L0806: 2, L0518: 2, L0663: 2, L0665: 2, H0659: 2, L0759: 2, S0436: 2, L0588: 2, L0605: 2, H0657: 1, S0356: 1, S0444: 1, H0747: 1, L0717: 1, L3388: 1,			

									H0600: 1, H0156: 1, H0251: 1, H0375: 1, S0003: 1, H0032: 1, H0634: 1, H0616: 1, H0561: 1, L3904: 1, L0773: 1, L0662: 1, L0768: 1, L0388: 1, L0775: 1, L0655: 1, L0661: 1, L0666: 1, S0053: 1, L0438: 1, H0547: 1, H0436: 1, S0037: 1, L0748: 1, L0779: 1, L0731: 1, L0758: 1, L0581: 1 and S0026: 1.			
204	HSIDJ81	589447	214	8 - 184	608	Glu-37 to Gly-45.			H0036: 1 and L0744: 1.			
205	HSJBQ79	1304677	215	41 - 586	609	Gly-16 to Arg-32, Ala-42 to Asn-50, Glu-66 to Gln-76, Arg-85 to Gly-94, Thr-108 to Asp-115, Trp-121 to Gly-130, Leu-137 to His-144, Glu-155 to Lys-161, Asp-175 to Ser-180.			S0356: 14, S0212: 4, S0040: 2, H0599: 2, H0551: 2, H0413: 2, S0210: 2, S0126: 2, S0027: 2, H0665: 2, S0196: 2, H0716: 1, S0418: 1, S0420: 1, H0550: 1, H0486: 1, H0013: 1, H0544: 1, H0546: 1, H0086: 1, H0286: 1, H0628: 1, L0654: 1, L0565: 1, H0689: 1, H0670: 1, H0660: 1, S0037: 1, S0028: 1, S0032: 1, L0595: 1, H0668: 1, H0667: 1, S0192: 1,			







									L0386: 1, L0774: 1, L0775: 1, L0375: 1, L0805: 1, L0776: 1, L0655: 1, L0783: 1, L0519: 1, L0367: 1, L0790: 1, L0666: 1, L0663: 1, L2263: 1, L0565: 1, S0148: 1, H0726: 1, H0724: 1, L0438: 1, H0519: 1, S0152: 1, S0454: 1, H0521: 1, H0696: 1, S3012: 1, S0124: 1, L0439: 1, L0750: 1, H0595: 1, S0436: 1, H0668: 1, H0667: 1, S0242: 1, S0276: 1 and L3603: 1.			
HSKDA27	1074734	374	127 - 1653	768	Gly-31 to Arg-36, Thr-55 to Glu-62, Ser-64 to Ser-79, Arg-87 to Asp-96, Arg-103 to Ala-109, Asp-120 to Arg-126, Gly-294 to Gly-302, Ser-305 to Ala-318, Val-320 to Arg-327, Pro-342 to Thr-351, Thr-383 to Thr-399, Leu-414 to Lys-435, Thr-449 to Ala-457, Gly-461 to Asn-479, Gly-483 to Gln-498,							





									H0494: 1, S0014: 1, H0625: 1, H0509: 1, H0641: 1, S0002: 1, L0637: 1, L3905: 1, L0646: 1, L0773: 1, L0662: 1, L0768: 1, L0652: 1, L0776: 1, L0659: 1, L0783: 1, S0374: 1, H0783: 1, H0593: 1, S0126: 1, H0659: 1, H0658: 1, H0648: 1, H0672: 1, S3012: 1, S0028: 1, L0754: 1, L0750: 1, L0731: 1, S0260: 1, S0436: 1, L0596: 1, L0581: 1, S0242: 1, S0194: 1, H0543: 1, S0446: 1, H0506: 1 and H0008: 1.				
	HSKGN81	409905	376	537 - 608	770	Thr-11 to Pro-22.							
208	HSKNB56	548077	218	484 - 741	612	Thr-23 to Pro-29, Thr-68 to Pro-76.	L0766: 8, L2439: 5, L0485: 4, S0003: 3, L0748: 3, L0731: 3, S0376: 2, S0360: 2, L0804: 2, L0659: 2, L0438: 2, L0751: 2, L0757: 2, H0556: 1, L2905: 1, H0730: 1, S0046: 1, H0747: 1, H0749: 1, H0411: 1, H0549: 1, S0222: 1, H0632: 1, L2495: 1,						

									L3655: 1, S0474: 1, H0596: 1, H0163: 1, H0494: 1, L0598: 1, L0772: 1, L0768: 1, L0803: 1, L0774: 1, L0775: 1, L0805: 1, L0655: 1, L0809: 1, L0663: 1, L0665: 1, L2440: 1, H0682: 1, H0672: 1, H0710: 1, H0521: 1, H0784: 1, S3012: 1, L3327: 1, L0750: 1, L0752: 1, L0758: 1, L0362: 1, H0506: 1 and H0721: 1.			
209	HSNAD72	467397	219	220 - 327	613				H0163: 2			
210	HSNMC45	1352201	220	225 - 389	614				H0163: 1			
	HSNMC45	545060	377	232 - 309	771							
211	HSQFP66	460537	221	96 - 332	615				S0007: 1, H0555: 1 and S0026: 1.			
212	HSRFZ57	892171	222	82 - 207	616				S0022: 4			
213	HSUBW09	413246	223	153 - 323	617				L0766: 5, L0749: 3, S0134: 2, L0770: 2, L0794: 2, L0809: 2, L0790: 2, H0556: 1, H0735: 1, L0622: 1, H0457: 1, H0561: 1, L0662: 1, L0804: 1, L5622: 1, H0436: 1, L0779: 1, L0731: 1, L0758: 1, H0136: 1 and H0506: 1.			

214	HSVBU91	596868	224	256 - 528	618	Asp-26 to Asn-31, Ser-37 to His-49, Ala-65 to Ser-73.	H0309: 1		
215	HSXGI47	886200	225	87 - 260	619		L0439: 15, L0752: 6, L0758: 6, L0438: 5, L0731: 5, L0803: 4, H0171: 3, L0717: 3, H0251: 3, L0142: 3, S0036: 3, S0422: 3, L0764: 3, L0659: 3, L0666: 3, L0664: 3, S0380: 3, L0754: 3, L0759: 3, L0591: 3, L0608: 3, H0624: 2, T0002: 2, H0486: 2, H0052: 2, L0471: 2, H0375: 2, S0002: 2, L0771: 2, L0766: 2, L0776: 2, L0657: 2, L0517: 2, L0665: 2, S0330: 2, S0028: 2, L0747: 2, L0749: 2, L0750: 2, H0445: 2, L0603: 2, H0170: 1, H0685: 1, L0785: 1, H0341: 1, S0298: 1, S0212: 1, S0282: 1, H0255: 1, S0418: 1, T0007: 1, S0358: 1, S0360: 1, H0580: 1, S0007: 1, S0045: 1, S0046: 1, H0393: 1, H0351: 1, H0441: 1,		





216	HSYAZ63	1177537	226	448 - 1749	620	Gln-14 to Thr-21, Arg-26 to Pro-31, Leu-43 to Pro-50, Leu-81 to Asp-88, Pro-153 to Thr-158, Leu-211 to Thr-222, Asp-228 to Asn-233, Pro-273 to Glu-282.	S0456: 1 and L0600: 1. H0521: 40, H0046: 18, H0522: 11, L0747: 8, L0750: 8, S0002: 7, L0439: 7, L0754: 7, H0486: 6, L0595: 6, H0556: 5, H0551: 5, H0024: 4, H0622: 4, S0344: 4, H0519: 4, L0740: 4, L0751: 4, L0759: 4, L0599: 4, H0580: 3, H0013: 3, H0581: 3, S0051: 3, L0369: 3, H0402: 2, S0356: 2, S0360: 2, S0045: 2, S0046: 2, H0411: 2, H0574: 2, L0021: 2, H0575: 2, H0594: 2, H0266: 2, S0214: 2, H0252: 2, H0090: 2, H0038: 2, H0616: 2, H0412: 2, S0038: 2, T0041: 2, H0561: 2, H0130: 2, S0426: 2, H0529: 2, L0800: 2, L0764: 2, L0794: 2, L0766: 2, L0775: 2, L0375: 2, L0806: 2, L0776: 2, L0526: 2, L0383: 2, L0789: 2, H0555: 2, L0741: 2, L0756: 2, L0758: 2, L0591: 2,		
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									L0542: 1, L0782: 1, L0809: 1, S0052: 1, S0053: 1, H0144: 1, S0126: 1, H0689: 1, S0332: 1, H0696: 1, H0134: 1, S0037: 1, S0027: 1, L0755: 1, L0757: 1, S0031: 1, H0445: 1, S0436: 1, L0593: 1, S0026: 1, H0543: 1 and H0506: 1.					
217	HSYAZ63	862063	378	215 - 337	772	Ser-22 to His-32.								
	HSYBG37	1056317	227	47 - 964	621	Ser-47 to Pro-57, Ser-77 to Glu-82, Thr-90 to Trp-98, Arg-124 to Lys-137, Ala-183 to Glu-192, Lys-220 to Gln-229, Asn-244 to Arg-258, Thr-271 to Asn-278, Glu-285 to Gly-297.								L0770: 3, S0442: 2, S0358: 2, L0769: 2, S0380: 2, H0717: 1, S6024: 1, H0656: 1, H0341: 1, H0409: 1, H0486: 1, L2637: 1, T0060: 1, H0156: 1, H0036: 1, H0421: 1, H0052: 1, H0544: 1, H0551: 1, H0059: 1, S0142: 1, L3904: 1, L3905: 1, L0378: 1, L5622: 1, L0709: 1, L2263: 1, L3811: 1, H0547: 1, L0602: 1, L0611: 1, L0742: 1, L0748: 1, L0439: 1, L0756: 1, L0777: 1, L0731: 1, S0434: 1 and L0599: 1.
	HSYBG37	581098	379	48 - 965	773	Ser-47 to Pro-57.								

218	HTADW91	844835	228	59 - 1150	622	Ser-77 to Glu-82, Thr-90 to Trp-98, Arg-124 to Lys-137, Ala-183 to Glu-192, Lys-220 to Gln-229, Asn-244 to Arg-258, Thr-271 to Asn-278, Glu-285 to Gly-297.	H0618: 12, L0743: 10, L0794: 9, L0803: 9, L0758: 9, L0731: 8, L0748: 7, L0754: 6, H0545: 5, H0658: 5, H0052: 4, H0546: 4, L0648: 4, L0662: 4, L0774: 4, L0665: 4, L0779: 4, H0135: 3, L0659: 3, H0547: 3, H0521: 3, L0751: 3, L0747: 3, H0295: 2, H0657: 2, H0306: 2, S0420: 2, S0356: 2, S0360: 2, H0549: 2, H0550: 2, H0253: 2, H0544: 2, H0424: 2, H0163: 2, H0551: 2, S0142: 2, L0770: 2, L0769: 2, L0766: 2, L0804: 2, L0806: 2, L0805: 2, L0809: 2, L5623: 2, L0789: 2, L0663: 2, H0690: 2, H0672: 2, S3014: 2,		
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									L2261: 1, L2716: 1, H0593: 1, H0435: 1, H0670: 1, H0660: 1, S0332: 1, S0406: 1, H0555: 1, L0610: 1, S0037: 1, L0744: 1, L0756: 1, L0752: 1, L0757: 1, S0434: 1, S0436: 1, L0588: 1, L0599: 1, L0601: 1, L0603: 1 and S0456: 1.				
219	HTAEE28	1018291	229	319 - 1167	623	Pro-255 to Leu-264.			H0250: 3, H0069: 2, L0771: 2, S0404: 2, H0650: 1, H0656: 1, H0486: 1, H0013: 1, H0318: 1, S0422: 1, L0644: 1, L0768: 1, L0794: 1, L0804: 1, L0655: 1, L0789: 1, L0664: 1, H0436: 1 and L0758: 1.				
	HTAEE28	882919	380	372 - 737	774								
	HTAEE28	864120	381	124 - 771	775								
220	HTDAF28	396835	230	38 - 301	624	Pro-22 to Glu-33.			H0551: 4, L0665: 3, S0356: 2, S0360: 2, L0662: 2, L0527: 2, L0666: 2, L0754: 2, H0333: 1, H0012: 1, H0688: 1, H0553: 1, H0477: 1, L0770: 1, L0769: 1, L0650: 1, L0606: 1, L0790: 1, H0520: 1, H0547: 1.				

221	HTECC05	1352365	231	13 - 546	625	Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Gly-122, Pro-156 to Trp-161.	H0682: 1, L0747: 1, L0779: 1 and L0755: 1. H0617: 10, S0410: 8, L0758: 8, L0769: 7, H0038: 6, L0439: 6, L0750: 6, L0752: 6, S0360: 5, L0775: 5, S0406: 5, H0150: 4, L0157: 4, H0620: 4, H0087: 4, S0440: 4, S0344: 4, L0763: 4, S0328: 4, L0747: 4, H0224: 3, H0484: 3, H0402: 3, S0049: 3, H0708: 3, L0773: 3, L0805: 3, L0809: 3, L0519: 3, H0670: 3, L0748: 3, L0731: 3, L0757: 3, L0581: 3, H0295: 2, H0341: 2, S0444: 2, S0222: 2, L0622: 2, H0253: 2, H0309: 2, T0115: 2, H0544: 2, H0545: 2, H0081: 2, H0012: 2, H0673: 2, S0036: 2, H0616: 2, L0770: 2, L0774: 2, L0518: 2, H0725: 2, S0374: 2, H0696: 2, L0588: 2, H0543: 2, L0615: 1, H0160: 1, H0225: 1, H0713: 1, S6024: 1,			
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									L0375: 1, L0806: 1, L0776: 1, L0517: 1, L0526: 1, L0783: 1, L0789: 1, H0144: 1, L0438: 1, H0689: 1, H0690: 1, H0682: 1, H0683: 1, H0435: 1, H0659: 1, H0648: 1, H0521: 1, H0522: 1, S3014: 1, S0027: 1, L0755: 1, L0759: 1, H0445: 1, H0343: 1, H0595: 1, L0608: 1, H0136: 1, S0276: 1, H0542: 1, L0600: 1 and H0352: 1.			
	HTECC05	877448	382	21 - 404	776	Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Pro-127.						
	HTECC05	666743	383	27 - 518	777	Gly-41 to Leu-46, Asp-67 to Thr-75, Ile-114 to Ala-123.						
222	HTEEB42	206980	232	59 - 952	626	Met-1 to His-7.	L0794: 4, H0624: 2, H0038: 2, L0375: 2, S0330: 2, L0750: 2, L0779: 2, H0031: 1, H0644: 1, H0124: 1, H0591: 1, H0616: 1, H0264: 1, H0623: 1, L0770: 1, L0637: 1, L0805: 1, L0663: 1, L0749: 1, L0777: 1, L0780: 1 and L0599: 1.					

223	HTEFU65	543396	233	231 - 371	627	Gly-35 to Gly-40.	H0486: 3, H0253: 1, H0544: 1, H0012: 1, S0388: 1, H0553: 1, H0090: 1, H0038: 1, H0652: 1, L0769: 1, L0641: 1, L0806: 1, H0696: 1, L0748: 1, L0749: 1, S0031: 1 and S0196: 1.		
224	HTEGA76	381995	234	90 - 284	628		H0038: 1 and L0758: 1.		
225	HTEJN13	1352272	235	156 - 779	629	Tyr-37 to Cys-49, Gly-51 to Tyr-56, Lys-88 to Trp-93, Phe-125 to Lys-140, Lys-147 to Thr-153, Thr-175 to Asn-188, Ala-203 to Met-208.	L0758: 4, L0770: 2, L0754: 2, L0779: 2, L3643: 1, H0327: 1, H0038: 1, L0769: 1, L0764: 1, L0794: 1, H0658: 1, L0748: 1, L0777: 1, L0780: 1, L0731: 1 and L0465: 1.		
	HTEJN13	658744	384	163 - 639	778	Tyr-37 to Cys-49, Gly-51 to Tyr-56, Lys-88 to Trp-93, Leu-130 to Glu-136.			
	HTEJN13	381941	385	155 - 367	779				
226	HTELP17	836072	236	164 - 298	630		L0758: 3, S0408: 2, H0031: 2, H0038: 2, L0766: 2, H0521: 2, L0748: 2, H0341: 1, L3659: 1, S0476: 1, H0581: 1, S0051: 1, H0266: 1, H0111: 1, H0616: 1, L0794: 1, L0805: 1, L0787: 1, L0779: 1, L0759: 1,		

									L0593: 1, H0542: 1 and H0543: 1.			
227	HTELS08	847090	237	15 - 491	631	Pro-98 to Gln-106.			H0616: 2, L0758: 2 and H0038: 1.			
228	HTLEP53	634852	238	73 - 378	632	Ser-33 to Lys-43.			H0253: 1			
229	HTOIY21	665745	239	91 - 783	633	Pro-22 to Pro-28, Pro-41 to His-48, Pro-79 to His-86, Pro-126 to Phe-134, Ser-137 to Met-143, Gln-176 to Ser-186.			S0114: 1 and H0264: 1.			
230	HTPCS72	854941	240	2365 - 2577	634				L0438: 6, L0439: 5, H0661: 3, L0776: 3, H0556: 2, H0100: 2, L0598: 2, L0764: 2, L0766: 2, H0672: 2, L0777: 2, L0731: 2, H0170: 1, H0171: 1, H0265: 1, H0140: 1, S0114: 1, H0657: 1, H0656: 1, H0638: 1, S0418: 1, S0408: 1, H0730: 1, H0741: 1, S0046: 1, H0411: 1, S0278: 1, H0550: 1, S0222: 1, T0104: 1, H0600: 1, S0280: 1, S0474: 1, H0007: 1, T0110: 1, H0046: 1, H0457: 1, H0150: 1, H0566: 1, H0620: 1, H0057: 1, H0039: 1, H0030: 1, L0055: 1,	1		



233	HTTBI76	637725	243	133 - 534	637	Glu-55 to Arg-61, Gln-84 to Ser-92, Ser-99 to Ser-104.	L0803: 4, L0731: 4, L0774: 3, S0380: 3, S0028: 3, L0758: 3, H0486: 2, S0003: 2, H0040: 2, S0344: 2, L0766: 2, L0775: 2, H0547: 2, L0748: 2, L0756: 2, L0777: 2, L0780: 2, L0753: 2, S0011: 2, H0716: 1, H0638: 1, L0617: 1, S0358: 1, H0411: 1, S0280: 1, H0318: 1, H0355: 1, H0674: 1, H0212: 1, H0135: 1, H0038: 1, H0132: 1, S0142: 1, S0002: 1, H0529: 1, L0804: 1, L0632: 1, L0666: 1, H0682: 1, H0684: 1, H0525: 1, S0044: 1, S0406: 1, H0555: 1, L0747: 1, L0750: 1, L0752: 1, L0755: 1, L0604: 1 and S0026: 1.		
234	HTTBS64	1008159	244	95 - 223	638	Leu-37 to Asn-42.	H0040: 1		
	HTTBS64	863187	389	100 - 228	783	Leu-37 to Asn-42.			
	HTTBS64	754125	390	175 - 402	784	Lys-41 to Arg-46.			
235	HTWKE60	634083	245	185 - 319	639		L0803: 10, L0748: 10, L0439: 8, L0438: 7, L0752: 7, H0013: 6, L0777: 6, L0593: 6, H0551: 5, L0740: 5,		

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									H0266: 1, S0003: 1, H0615: 1, H0070: 1, H0030: 1, H0628: 1, H0032: 1, H0598: 1, H0591: 1, H0038: 1, H0264: 1, H0494: 1, S0440: 1, L0773: 1, L0662: 1, L0363: 1, L0804: 1, L0650: 1, L0375: 1, L0805: 1, L0776: 1, L0655: 1, L0658: 1, L0783: 1, L0809: 1, L5622: 1, L0791: 1, L0666: 1, S0053: 1, L2257: 1, L2258: 1, S0374: 1, L3826: 1, H0520: 1, S0126: 1, H0658: 1, H0660: 1, H0521: 1, H0555: 1, H0576: 1, S0037: 1, L0741: 1, L0750: 1, L0753: 1, L0731: 1, S0031: 1, H0445: 1, L0686: 1, L0589: 1, L0599: 1, H0136: 1, S0194: 1, L3378: 1 and L3631: 1.					
236	HTXAJ12	1310814	246	91 - 426	640	Lys-99 to Arg-107.		H0265: 1 and H0264: 1.						
	HTXAJ12	567434	391	91 - 426	785	Lys-99 to Arg-107.								
237	HTXJM03	603918	247	328 - 498	641	Asp-51 to His-56.		L0766: 5, H0313: 3, H0624: 1, H0265: 1, H0556: 1, S0116: 1, H0329: 1, H0486: 1,						

238	HTXKF95	891275	248	421 - 657	642	Met-1 to Pro-6, Gly-73 to Thr-78.	H0156: 1, H0590: 1, H0009: 1, S0250: 1, H0169: 1, S0450: 1, S0002: 1, L0769: 1, L0793: 1, L0532: 1, L0750: 1, L0777: 1 and S0424: 1.  L0754: 41, L0747: 8, L0755: 5, L0659: 4, H0265: 2, H0556: 2, H0586: 2, L0471: 2, H0553: 2, L0764: 2, L0662: 2, L0794: 2, L0748: 2, L0751: 2, L0749: 2, L0750: 2, H0305: 1, S0358: 1, S0046: 1, H0441: 1, H0599: 1, H0569: 1, H0050: 1, H0051: 1, H0030: 1, H0124: 1, H0616: 1, L0770: 1, L0769: 1, L0800: 1, L0644: 1, L0363: 1, L0803: 1, L0804: 1, L0775: 1, L0806: 1, L0783: 1, L0666: 1, L0665: 1, H0144: 1, H0555: 1, S3012: 1, L0779: 1, L0731: 1, L0605: 1, L0599: 1, L0603: 1, H0543: 1, H0422: 1 and H0506: 1.		
	HTXKF95	834438	392	330 - 566	786	Met-1 to Pro-6,			





									T0042: 1, S0344: 1, S0422: 1, S0002: 1, L0775: 1, L0806: 1, L0805: 1, L0776: 1, S0152: 1, H0704: 1, H0555: 1, H0436: 1, L0439: 1, L0751: 1, L0752: 1, L0731: 1, L0588: 1, L0592: 1, S0026: 1, H0543: 1 and H0423: 1.			
242	HWAAD63	838626	252	322 - 825	646	Pro-53 to Trp-61.			H0441: 1, H0581: 1 and H0604: 1.			
	HWAAD63	833089	393	322 - 483	787							
	HWAAD63	793875	394	312 - 818	788							
243	HWADJ89	799506	253	581 - 709	647				H0581: 1			
244	HWBCP79	846382	254	243 - 560	648	Trp-47 to Thr-54, Ser-68 to Asn-73, Ser-86 to Gly-92.			H0580: 1 and H0169: 1.			
	HWBCP79	646977	395	233 - 550	789	Trp-47 to Thr-54.						
245	HWBEM18	949402	255	75 - 5738	649	Ser-165 to His-174, Met-196 to Asp-204, Lys-212 to Leu-218, Pro-277 to Leu-285, Pro-290 to Arg-298, Ser-402 to Ser-407, Trp-465 to Gly-470, His-698 to His-706, Asp-793 to Asn-801, Gln-830 to Lys-838, Gly-862 to His-867, Ala-871 to His-877, Lys-1063 to Asn-1069,			H0556: 7, H0581: 5, H0265: 4, H0083: 4, H0424: 4, H0543: 4, H0580: 3, H0318: 3, L0766: 3, L0783: 3, H0422: 3, H0650: 2, L2599: 2, H0069: 2, H0635: 2, H0457: 2, H0620: 2, H0634: 2, L3144: 2, L0764: 2, L0666: 2, L0758: 2, H0740: 1, H0656: 1, H0341: 1, L3684: 1,			

						Ser-1100 to Ser-1108, Asn-1194 to Ser-1200, Leu-1308 to Gly-1314, Lys-1437 to Asn-1442, Asp-1583 to Val-1599, Thr-1651 to Lys-1656, Lys-1735 to Gly-1740, Arg-1789 to Tyr-1795, Arg-1846 to His-1854, Pro-1869 to Pro-1875.	H0637: 1, H0645: 1, H0393: 1, L3312: 1, H0610: 1, H0333: 1, H0618: 1, H0309: 1, H0009: 1, H0050: 1, H0051: 1, H0290: 1, H0617: 1, S0038: 1, S0426: 1, H0529: 1, L0770: 1, L0761: 1, L0667: 1, L0772: 1, L0646: 1, L0642: 1, L0643: 1, L0773: 1, L0774: 1, L0655: 1, L0558: 1, L0665: 1, H0701: 1, L2467: 1, L0438: 1, L2681: 1, H0520: 1, H0670: 1, H0521: 1, H0522: 1, H0134: 1, L0748: 1, L0439: 1, L0751: 1, L0756: 1, H0445: 1, S0436: 1 and H0216: 1.			
	HWBEM18	906580	396	65 - 2725	790					
	HWBEM18	877573	397	1 - 1494	791					
246	HWBFX31	799427	256	271 - 426	650		L0659: 5, L0794: 4, L0809: 4, L0777: 4, H0424: 3, L0766: 3, L0745: 3, H0265: 2, H0656: 2, H0254: 2, H0662: 2, S0376: 2, H0457: 2, H0024: 2, L0768: 2, H0670: 2, H0555: 2, L0751: 2,			



								Pro-265 to Pro-273, Pro-275 to Val-284, Ala-288 to Arg-295, Gln-304 to Gly-325.	L0776: 2, L0809: 2, H0696: 2, L0731: 2, H0556: 1, H0295: 1, H0177: 1, H0638: 1, H0370: 1, H0592: 1, H0587: 1, H0486: 1, L2539: 1, L0021: 1, H0081: 1, H0271: 1, H0181: 1, H0617: 1, H0380: 1, L0653: 1, L0659: 1, L0783: 1, L5622: 1, L0789: 1, L0791: 1, S0328: 1, L0752: 1, L0601: 1 and L3603: 1.			
248	HWTBK81	460568	258	139 - 606	652			Tyr-59 to Gln-68, His-84 to Leu-90, Ser-105 to Asn-110, Leu-112 to Pro-118.	L0439: 4, L0748: 2, H0351: 1, S0364: 1, L0768: 1, L0650: 1, L0375: 1, L0747: 1 and H0352: 1.			
249	HAGAI85	381942	259	166 - 255	653			Ser-24 to Trp-30.	L0754: 14, H0575: 4, L0742: 3, L0752: 3, S0010: 2, H0494: 2, H0521: 2, L0748: 2, L0749: 2, L0758: 2, L0759: 2, H0445: 2, H0220: 1, H0402: 1, S0376: 1, S0132: 1, H0250: 1, H0581: 1, H0052: 1, S0051: 1, H0356: 1, H0375: 1, H0039: 1, H0644: 1, H0628: 1, S0036: 1,			



	HOFOC33	806819	403	3 - 866	797				
251	HSDEZ20	1352287	261	58 - 423	655	Phe-8 to Ser-13, Val-81 to Arg-87, Asp-98 to Pro-104.	S0031: 1		
	HSDEZ20	704101	404	66 - 359	798	Phe-8 to Ser-13, Ala-84 to Ser-90.			

Table 1B.2

Gene No:	cDNA Clone ID	Contig ID:	SEQ ID NO:X	Tissue Distribution Library Code:Count (see Table 4 for Library Codes)
1	H2CBU83	884134	11	AR182:8, AR314:7, AR271:7, AR280:6, AR315:6, AR052:6, AR224:6, AR225:5, AR164:5, AR215:5, AR270:5, AR165:5, AR162:5, AR310:5, AR245:5, AR166:5, AR161:5, AR169:5, AR223:5, AR266:5, AR172:5, AR039:5, AR192:5, AR163:4, AR193:4, AR207:4, AR176:4, AR269:4, AR175:4, AR226:4, AR243:4, AR217:4, AR273:4, AR168:4, AR282:4, AR204:4, AR291:4, AR265:4, AR183:4, AR274:4, AR299:4, AR214:4, AR205:4, AR206:4, AR194:4, AR060:4, AR272:4, AR238:4, AR186:4, AR222:4, AR053:4, AR197:4, AR089:3, AR257:3, AR295:3, AR289:3, AR311:3, AR221:3, AR171:3, AR191:3, AR250:3, AR235:3, AR252:3, AR275:3, AR309:3, AR177:3, AR180:3, AR173:3, AR178:3, AR246:3, AR312:3, AR188:3, AR292:3, AR298:3, AR284:3, AR212:3, AR201:3, AR285:3, AR189:3, AR296:3, AR181:3, AR300:3, AR185:3, AR253:3, AR202:3, AR281:3, AR237:3, AR184:3, AR268:3, AR233:3, AR286:3, AR232:3, AR308:3, AR277:3, AR267:3, AR228:3, AR288:3, AR316:3, AR239:3, AR195:2, AR242:2, AR263:2, AR033:2, AR287:2, AR196:2, AR210:2, AR259:2, AR174:2, AR294:2, AR096:2, AR234:2, AR293:2, AR290:2, AR190:2, AR255:2, AR055:2, AR213:2, AR264:2, AR231:2, AR313:2, AR297:2, AR258:2, AR170:2, AR218:2, AR247:2, AR061:2, AR236:2, AR219:2, AR198:2, AR230:2, AR254:2, AR256:2, AR261:2, AR104:2, AR240:2, AR262:2, AR283:2, AR229:2, AR227:2, AR260:2, AR200:1, AR203:1, AR179:1, AR244:1, AR199:1 S0414:9, S0422:7, L0662:7, S0444:6, L0748:4, L0581:4, S0442:3, H0031:3, L0666:3, L0754:3, H0656:2, S0358:2, S0360:2, H0013:2, S0438:2, S0440:2, L0598:2, L0803:2, L0540:2, L0756:2, L0752:2, L0758:2, L0759:2, S0242:2, H0624:1, S0282:1, H0742:1, H0393:1, H0586:1, H0574:1, H0036:1, H0004:1, T0103:1, T0110:1, H0571:1, H0569:1, H0123:1, L0471:1, H0594:1, S6028:1, H0622:1, UNKWN:1, L0649:1, L0381:1, L0776:1, L0659:1, L0528:1, L0792:1, L0793:1, L0663:1, L0664:1, L0665:1, L2257:1, H0144:1, S0374:1, H0547:1, H0593:1, H0690:1, H0670:1, H0648:1, H0672:1, H0651:1, H0539:1, S0378:1, S0380:1, H0521:1, S0406:1, H0555:1, H0478:1, L0744:1, L0731:1 and S0276:1.
	H2CBU83	745366	259	
2	H6EDC19	543259	12	AR235:21, AR197:20, AR222:17, AR261:13, AR309:11, AR195:11, AR176:9, AR201:9, AR264:9, AR295:9, AR162:9, AR271:9, AR242:9, AR161:9, AR163:9, AR177:9, AR165:9, AR089:9, AR236:8, AR164:8, AR283:8, AR252:8, AR196:8, AR166:8, AR296:8, AR229:8, AR198:8, AR263:7, AR297:7, AR181:7, AR269:7, AR287:7, AR289:7, AR288:7, AR245:7, AR285:7, AR253:7, AR060:7, AR204:7, AR183:7, AR266:7, AR268:6, AR240:6, AR180:6, AR312:6, AR246:6, AR192:6, AR199:6, AR055:6, AR316:6, AR247:6, AR272:6, AR178:6, AR193:6, AR233:6, AR299:6, AR212:6, AR228:6, AR275:5, AR293:5, AR096:5, AR313:5, AR291:5, AR179:5, AR238:5, AR239:5, AR053:5, AR182:5, AR286:5, AR237:5, AR231:5, AR308:5, AR274:5, AR250:5, AR185:5, AR226:5, AR205:5, AR270:5, AR104:5, AR255:5, AR257:5, AR218:5, AR175:5, AR190:4, AR061:4, AR219:4, AR191:4, AR262:4, AR203:4, AR217:4, AR213:4, AR174:4, AR267:4, AR243:4, AR039:4, AR230:4, AR033:4, AR188:4, AR311:4, AR232:4, AR234:4, AR254:4, AR300:4, AR189:4, AR168:4, AR214:4, AR207:3, AR227:3, AR277:3, AR173:3, AR294:3, AR211:3, AR258:3, AR170:3, AR282:3, AR171:3, AR200:3, AR225:3, AR223:3, AR290:3, AR260:2, AR224:2, AR216:2, AR210:2, AR172:2, AR215:1, AR169:1 L0805:4, H0559:3, L0803:3, H0545:2, L0664:2,



3	HACBD91	637482	13	L0748:2, L0777:2, L3643:1, H0295:1, H0657:1, S0444:1, H0734:1, H0550:1, S0222:1, T0048:1, H0318:1, H0052:1, H0231:1, H0041:1, H0620:1, H0606:1, H0316:1, H0077:1, L0769:1, L0761:1, L0766:1, L0774:1, L0789:1, H0672:1, H0539:1, S0146:1, L0751:1, L0780:1, L0731:1, S0434:1 and S0196:1. AR055:116, AR283:103, AR060:91, AR089:55, AR235:53, AR299:52, AR185:51, AR104:49, AR096:34, AR039:30, AR282:30, AR316:29, AR261:29, AR196:24, AR218:23, AR219:21, AR272:20, AR300:20, AR313:19, AR277:19, AR240:19, AR309:17, AR236:17, AR295:16, AR252:15, AR271:15, AR191:15, AR285:14, AR246:13, AR165:13, AR291:13, AR264:13, AR311:13, AR164:13, AR166:13, AR308:12, AR275:12, AR174:12, AR287:11, AR263:11, AR286:11, AR177:11, AR161:10, AR162:10, AR200:10, AR201:10, AR163:10, AR195:10, AR262:10, AR188:10, AR207:10, AR288:10, AR267:10, AR197:9, AR181:9, AR266:9, AR312:9, AR227:9, AR257:9, AR175:9, AR289:9, AR232:9, AR189:8, AR297:8, AR053:8, AR033:8, AR190:8, AR245:8, AR296:8, AR193:8, AR258:8, AR255:8, AR239:7, AR260:7, AR173:7, AR198:7, AR293:7, AR199:7, AR250:7, AR243:6, AR247:6, AR274:6, AR211:6, AR205:6, AR203:6, AR213:6, AR178:6, AR226:5, AR256:5, AR231:5, AR294:5, AR270:5, AR204:5, AR176:5, AR238:5, AR210:5, AR230:4, AR237:4, AR253:4, AR170:4, AR212:4, AR061:4, AR183:4, AR242:4, AR254:3, AR169:3, AR182:3, AR290:3, AR268:3, AR179:3, AR221:2, AR216:2, AR168:2, AR224:2, AR229:2, AR214:2, AR223:1, AR228:1, AR172:1, AR192:1, L0748:8, L0439:4, L0749:3, H0171:2, L3659:2, L0438:2, S6024:1, S0360:1, H0640:1, S0278:1, L3655:1, S0280:1, H0012:1, L0055:1, H0032:1, H0647:1, L0807:1, L0665:1, H0659:1, L0355:1, S0328:1, H0754:1, H0710:1, L0756:1, L0780:1, L0759:1, S0260:1, S0452:1 and H0721:1.
4	HACCI17	891114	14	AR251:15, AR310:9, AR273:8, AR265:7, AR248:6, AR241:5, AR052:5, AR312:5, AR274:5, AR215:5, AR313:4, AR263:4, AR309:4, AR170:4, AR243:4, AR235:4, AR053:4, AR213:4, AR249:3, AR271:3, AR184:3, AR206:3, AR198:3, AR292:3, AR282:3, AR266:3, AR284:3, AR186:3, AR247:3, AR219:2, AR240:2, AR172:2, AR175:2, AR269:2, AR182:2, AR225:2, AR183:2, AR253:2, AR238:2, AR218:2, AR242:2, AR096:2, AR089:2, AR177:2, AR286:2, AR161:2, AR277:2, AR259:2, AR033:2, AR299:2, AR060:1, AR245:1, AR291:1, AR290:1, AR293:1, AR300:1, AR285:1, AR311:1, AR171:1, AR185:1, AR270:1, AR178:1, AR217:1, AR268:1, AR061:1, AR294:1, AR295:1, AR256:1, AR237:1, AR193:1, AR257:1, AR289:1, AR275:1, AR296:1, AR199:1, AR283:1, L0809:11, L0794:10, L0770:9, S0474:5, L0777:5, H0739:4, H0177:4, H0575:4, H0623:4, L0769:4, L0731:4, L0803:3, L0806:3, L0789:3, L0747:3, S6026:2, S0222:2, H0586:2, H0013:2, H0599:2, S0049:2, H0052:2, S0051:2, S0036:2, L3904:2, L5575:2, L3905:2, L0774:2, L0805:2, L0710:2, H0539:2, L0743:2, L0439:2, L0756:2, L0779:2, L0780:2, H0624:1, H0171:1, S0046:1, H0587:1, H0486:1, S0280:1, H0036:1, H0253:1, H0309:1, H0123:1, H0375:1, S6028:1, H0687:1, H0424:1, H0708:1, H0163:1, H0063:1, H0743:1, L5565:1, L0800:1, L0783:1, L5622:1, L0665:1, S0216:1, H0693:1, L0438:1, H0520:1, H0593:1, S0378:1, S0044:1, H0555:1, S0037:1, L0742:1, L0748:1, L0749:1, L0750:1, L0758:1, L0759:1, S0260:1 and L0599:1.
5	HACCI17 HAGAQ26	731877 561996	260 15	AR242:9, AR192:9, AR162:8, AR161:8, AR197:8, AR163:8, AR198:7, AR204:7, AR176:7, AR201:7, AR165:7, AR089:6, AR164:6, AR166:6, AR252:6, AR269:6, AR180:6, AR207:6, AR182:6, AR250:6, AR271:5, AR173:5, AR243:5, AR291:5, AR229:5, AR212:5, AR312:5, AR295:5, AR272:5, AR288:5, AR268:5, AR313:5, AR205:5, AR178:5, AR193:5, AR053:5, AR264:5, AR175:5, AR239:5, AR293:5, AR060:5, AR263:5, AR246:4, AR270:4,

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13	HAMFE15	905695	23	<p> IT0010:4, H0560:4, L0794:4, S0420:3, L0455:3, L3905:3, H0656:2, S0212:2, H0619:2, H0497:2, H0052:2, H0012:2, H0429:2, L0766:2, L5623:2, L0439:2, H0665:2, H0556:1, H0717:1, H0650:1, S0418:1, H0580:1, H0728:1, H0735:1, H0734:1, H0370:1, H0392:1, H0333:1, H0013:1, H0635:1, H0505:1, H0581:1, H0569:1, H0050:1, H0373:1, S0250:1, S0022:1, H0553:1, L0370:1, H0561:1, L2263:1, L2261:1, H0520:1, H0593:1, S0126:1, H0435:1, H0518:1, H0521:1, H0626:1, L0748:1, S0436:1, L0591:1, H0542:1, S0424:1 and H0677:1.  AR235:3, AR275:3, AR221:3, AR282:2, AR207:2, AR291:2, AR180:2, AR286:2, AR173:2, AR178:2, AR225:2, AR243:2, AR272:1, AR176:1, AR181:1, AR163:1, AR161:1, AR285:1, AR168:1, AR257:1, AR277:1, AR261:1, AR191:1, AR311:1, AR196:1, AR216:1, AR296:1, AR297:1, AR269:1, AR169:1, AR266:1, AR247:1, AR199:1, AR175:1 L0748:10, L0754:9, L0731:9, L0766:8, L0439:7, L0803:6, H0624:5, L0759:5, S0356:4, H0486:4, H0090:4, L0789:4, L0438:4, L0740:4, L0749:4, L0756:4, L0777:4, L0599:4, S0360:3, H0013:3, S0003:3, L0369:3, L0794:3, L0659:3, L0809:3, L0665:3, H0539:3, L0362:3, S0114:2, S0358:2, S0278:2, H0441:2, H0586:2, H0333:2, H0581:2, H0328:2, H0553:2, H0529:2, L0770:2, L0662:2, L0804:2, L0666:2, L0663:2, H0547:2, H0519:2, H0659:2, H0670:2, S0330:2, L0747:2, L0750:2, L0755:2, L0758:2, L0589:2, L0592:2, L0581:2, L0593:2, S0276:2, S0424:2, H0170:1, H0171:1, S0040:1, S0116:1, H0664:1, H0458:1, H0638:1, H0192:1, S0418:1, S0354:1, S0410:1, H0580:1, S0046:1, H0393:1, L0717:1, H0411:1, S0222:1, S0221:1, H0587:1, T0114:1, L0021:1, H0318:1, H0421:1, H0052:1, H0251:1, H0544:1, H0572:1, H0566:1, L0471:1, H0057:1, H0051:1, H0510:1, S0628:1, H0271:1, S0334:1, H0622:1, S0368:1, H0031:1, L0142:1, H0032:1, H0124:1, H0316:1, H0591:1, H0616:1, L0060:1, H0551:1, H0264:1, H0412:1, H0413:1, L0564:1, H0560:1, S0150:1, H0646:1, S0144:1, H0538:1, L0598:1, L0638:1, L0372:1, L0764:1, L0771:1, L0521:1, L0650:1, L0805:1, L0655:1, L0656:1, L0664:1, H0144:1, S0374:1, H0691:1, H0520:1, H0689:1, H0658:1, H0672:1, S0152:1, S0332:1, H0521:1, H0134:1, H0631:1, S0206:1, L0751:1, L0779:1, L0753:1, H0445:1, S0394:1, L0608:1, S0026:1, H0653:1, H0665:1, S0242:1, S0194:1, H0542:1, H0423:1 and H0422:1. </p>
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15	HAPBS03	656755	25		AR218:47, AR219:45, AR313:38, AR316:26, AR089:22, AR096:20, AR039:18, AR299:18, AR185:16, AR300:13, AR104:13, AR240:11, AR055:11, AR277:10, AR060:8, AR282:8, AR283:5 S0422:15, L0766:8, H0014:6, L0005:5, S0360:5, L3827:5, H0657:4, L0789:4, H0413:3, L0646:3, L0805:3, L0655:3, L0777:3, L0591:3, S0242:3, H0543:3, L3643:2, S0442:2, S0376:2, L0770:2, L0764:2, L0649:2, L0650:2, L0775:2, L0659:2, L0783:2, L0663:2, L0665:2, L3832:2, H0696:2, L0751:2, L0747:2, L0758:2, L0596:2, H0352:2, H0170:1, H0656:1, S0420:1, S0354:1, H0637:1, S0045:1, H0749:1, H0393:1, S0300:1, L0717:1, L3816:1, H0486:1, H0042:1, H0575:1, H0004:1, H0318:1, H0052:1, H0046:1, L0157:1, H0017:1, H0356:1, H0355:1, H0644:1, H0180:1, H0068:1, T0067:1, H0561:1, L5575:1, H0046:1, L0662:1, L0803:1, L0804:1, L0776:1, L0606:1, L0661:1, L0657:1, L0656:1, L0809:1, L0532:1, L2262:1, L0771:1, L0662:1, L0803:1, L0804:1, L0776:1, L0606:1, L0661:1, L0657:1, L0656:1, L0809:1, L0532:1, L2262:1, L3828:1, H0659:1, S0378:1, S0380:1, H0710:1, H0521:1, H0694:1, S0406:1, L0748:1, L0740:1, L0754:1, L0750:1, L0752:1, L0731:1, H0445:1, S0436:1, L0485:1, L0608:1, L0593:1, L0595:1, S0026:1, H0667:1 and S0424:1.
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31	HCE5F43	612796	41		AR060:280, AR055:230, AR299:151, AR089:139, AR104:127, AR283:124, AR185:112, AR039:97, AR096:88, AR316:79, AR282:66, AR277:62, AR300:50, AR240:46, AR218:40, AR219:35, AR313:29, AR215:8, AR169:8, AR221:8, AR217:8, AR214:7, AR216:7, AR225:7, AR171:6, AR222:5, AR223:5, AR246:5, AR188:5, AR263:5, AR224:5, AR245:5, AR191:5, AR269:5, AR168:5, AR270:5, AR205:5, AR183:5, AR176:4, AR252:4, AR166:4, AR190:4, AR175:4, AR235:4, AR165:4, AR178:4, AR266:4, AR164:4, AR170:4, AR180:4, AR274:4, AR179:4, AR174:4, AR196:4, AR192:4, AR163:4, AR161:4, AR162:4, AR275:4, AR309:4, AR193:4, AR264:4, AR257:4, AR053:4, AR181:4, AR201:4, AR189:4, AR312:3, AR271:3, AR311:3, AR195:3, AR173:3, AR033:3, AR177:3, AR295:3, AR268:3, AR210:3, AR291:3, AR197:3, AR288:3, AR203:3, AR200:3, AR182:3, AR272:3, AR290:3, AR308:3, AR285:3, AR236:3, AR198:3, AR255:3, AR243:3, AR231:3, AR250:3, AR294:3, AR172:2, AR287:2, AR286:2, AR238:2, AR237:2, AR226:2, AR289:2, AR254:2, AR297:2, AR296:2, AR204:2, AR247:2, AR260:2, AR262:2, AR293:2, AR239:2, AR261:2, AR233:2, AR229:2, AR232:2, AR267:2, AR211:2, AR234:2, AR212:2, AR256:1, AR258:1 L0777:10, L0756:4, S0414:3, L0659:3, L0740:3, H0441:2, S0003:2, H0616:2, L0766:2, H0144:2, L0439:2, L0780:2, L0759:2, L0596:2, S0242:2, H0542:2, S0470:1, S0342:1, H0341:1, S0001:1, S0282:1, S0408:1, S0007:1, T0060:1, H0427:1, H0098:1, H0042:1, H0581:1, H0049:1, H0052:1, H0024:1, H0051:1, H0647:1, S0422:1, L0770:1, L0769:1, L0772:1, L0662:1, L0794:1, L0803:1, L0805:1, L0666:1, L0663:1, L0664:1, S0374:1, S0126:1, H0648:1, H0696:1, L0747:1, L0752:1, L0755:1 and L0591:1.
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34	HCEWE20	543370	44		AR253:8, AR053:6, AR196:6, AR198:5, AR191:5, AR313:5, AR245:4, AR181:4, AR174:4, AR195:4, AR189:3, AR096:3, AR089:3, AR213:3, AR177:3, AR270:3, AR254:3, AR300:3, AR269:3, AR224:3, AR247:3, AR188:2, AR275:2, AR175:2, AR226:2, AR165:2, AR171:2, AR312:2, AR179:2, AR162:2, AR180:2, AR164:2, AR299:2, AR161:2, AR163:2, AR257:2, AR238:2, AR166:2, AR240:2, AR185:2, AR268:2, AR207:2, AR223:2, AR199:2, AR060:2, AR178:2, AR316:2, AR204:2, AR173:2, AR295:2, AR200:2, AR183:2, AR212:2, AR309:2, AR233:2, AR216:2, AR229:1, AR294:1, AR237:1, AR290:1, AR235:1, AR228:1, AR288:1, AR234:1, AR201:1, AR168:1, AR289:1, AR293:1, AR286:1, AR222:1, AR236:1, AR258:1, AR182:1, AR033:1, AR287:1, AR283:1, AR282:1, AR266:1, AR232:1, AR262:1, AR230:1 H0052:2, H0261:1, H0271:1 and S0458:1.
35	HCFOM18	553582	45		AR171:4, AR309:4, AR165:3, AR162:3, AR161:3, AR164:3, AR313:3, AR166:3, AR163:3, AR183:3, AR240:3, AR205:2, AR039:2, AR089:2, AR238:2, AR104:2, AR053:2, AR217:2, AR096:2, AR282:2, AR193:2, AR242:2, AR236:2, AR213:2, AR257:2, AR300:2, AR176:2, AR285:2, AR272:2, AR267:2, AR283:2, AR261:2, AR293:2, AR299:2, AR168:2, AR271:2, AR268:2, AR275:2, AR212:2, AR277:1, AR214:1, AR033:1, AR274:1, AR237:1, AR296:1, AR316:1, AR311:1, AR228:1, AR247:1, AR264:1, AR175:1, AR234:1, AR182:1, AR185:1, AR229:1, AR170:1, AR225:1, AR269:1, AR291:1, AR060:1, AR224:1, AR262:1, AR297:1, AR181:1, AR216:1, AR227:1, AR230:1, AR289:1 H0423:1
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37	HCNDR47	1016919	47		AR282:5, AR060:5, AR309:4, AR055:4, AR266:4, AR162:4, AR213:4, AR161:4, AR163:4, AR225:4, AR254:3, AR270:3, AR177:3, AR207:3, AR300:3, AR176:3, AR089:3, AR192:3, AR263:2, AR221:2, AR172:2, AR198:2, AR104:2, AR224:2, AR283:2, AR240:2, AR277:2, AR185:2, AR165:2, AR218:2, AR164:2, AR197:2, AR166:2, AR096:2, AR299:2, AR275:2, AR269:2, AR236:2, AR168:2, AR316:2, AR288:2, AR313:2, AR171:2, AR217:2, AR183:2, AR308:2, AR257:2, AR039:2, AR296:2, AR272:2, AR264:1, AR033:1, AR261:1, AR311:1, AR246:1, AR212:1, AR286:1, AR289:1, AR255:1, AR231:1, AR237:1, AR061:1, AR179:1, AR238:1, AR297:1, AR245:1, AR195:1, AR215:1 L0794:3, L0764:2, L0439:2, H0052:1, H0597:1, T0006:1, L0766:1, H0648:1, S0330:1 and L0753:1.
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38	HCNSB61	526413	48		AR235:4, AR180:3, AR282:3, AR192:2, AR197:2, AR295:2, AR266:2, AR271:2, AR060:2, AR162:1, AR161:1, AR163:1, AR170:1, AR089:1, AR169:1, AR257:1, AR261:1, AR217:1, AR168:1, AR277:1, AR225:1, AR311:1,

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40	HCQCT05	906285	276	
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41	HCUIM65	550208	51	AR223:4, AR215:3, AR268:3, AR270:3, AR250:3, AR161:3, AR246:3, AR162:3, AR166:2, AR171:2, AR254:2, AR217:2, AR213:2, AR177:2, AR089:2, AR243:2, AR290:2, AR257:2, AR269:2, AR288:1, AR313:1, AR179:1, AR205:1, AR309:1, AR165:1, AR163:1, AR170:1, AR261:1, AR225:1, AR195:1, AR240:1, AR181:1, AR238:1, AR193:1, AR299:1 L0789:4, L0809:2, L0759:2, L0596:2, H0306:1, H0402:1, H0580:1, H0550:1, H0370:1, H0404:1, H0559:1, H0486:1, H0031:1, H0674:1, H0135:1, H0100:1, L0800:1, L0794:1, L0804:1, L0805:1, L0515:1, L0783:1, H0672:1, L0777:1, H0444:1 and H0352:1.
42	HCWDS72	707833	52	AR194:5, AR162:5, AR241:4, AR215:4, AR249:4, AR313:3, AR221:3, AR207:3, AR310:3, AR169:3, AR265:3, AR229:3, AR183:3, AR298:2, AR282:2, AR284:2, AR291:2, AR292:2, AR270:2, AR312:2, AR223:2, AR165:2, AR273:2, AR182:2, AR164:2, AR227:2, AR240:2, AR289:2, AR166:2, AR172:2, AR266:2, AR246:2, AR061:2, AR222:2, AR293:2, AR269:2, AR053:2, AR171:2, AR238:2, AR295:2, AR271:1, AR177:1, AR163:1, AR299:1, AR052:1, AR290:1, AR039:1, AR231:1, AR296:1, AR096:1, AR178:1, AR186:1, AR232:1, AR294:1, AR285:1, AR286:1, AR192:1, AR233:1, AR268:1, AR247:1, AR161:1, AR230:1, AR274:1, AR226:1, AR210:1, AR300:1, AR089:1, AR311:1, AR277:1, AR234:1, AR237:1, AR193:1, AR206:1, AR259:1, AR201:1, AR168:1, AR216:1 L0752:30, L0754:17, L0740:16, H0521:14, L0439:14, L0766:12, S0003:11, S0214:11, L0777:10, S0002:8, L0770:8, L0776:8, L0748:8, L0755:8, S0360:7, L0665:7, L0757:7, T0067:6, S0440:6, L0666:6, L0747:6, L0774:5, L0751:5, S0222:4, H0575:4, H0622:4, L0662:4, L0775:4, H0547:4, S0126:4, S0380:4, L0750:4, S0436:4, L0362:4,

43	HCWKC15	553621	53	<p>H0638:3, H0580:3, H0494:3, S0422:3, L0598:3, S0374:3, H0710:3, H0522:3, H0555:3, L0356:3, L0756:3, L0780:3, L0731:3, L0759:3, L0594:3, S0134:2, S0376:2, S0046:2, H0393:2, S0278:2, H0438:2, H0586:2, L2477:2, H0156:2, S0474:2, H0581:2, H0421:2, T0110:2, L0471:2, S6028:2, S0022:2, H0090:2, H0591:2, H0040:2, H0551:2, H0412:2, L0520:2, L0764:2, L0768:2, L0803:2, L0655:2, L0659:2, L0664:2, L0438:2, H0648:2, H0672:2, S0406:2, S0028:2, L0588:2, L0599:2, H0667:2, S0196:2, H0624:1, H0171:1, H0265:1, S0040:1, H0713:1, S0114:1, L0811:1, H0341:1, S0212:1, S0001:1, H0661:1, H0305:1, S0418:1, L3649:1, H0741:1, S0045:1, H0747:1, S0132:1, S0476:1, L3089:1, H0619:1, H0415:1, H0409:1, L1942:1, L2495:1, L3655:1, H0013:1, S0010:1, S0665:1, H0327:1, H0046:1, L0157:1, S0051:1, T0010:1, H0266:1, H0179:1, H0615:1, H0096:1, H0031:1, H0553:1, L0055:1, H0674:1, H0163:1, H0038:1, H0264:1, H0413:1, L0564:1, H0560:1, H0359:1, H0509:1, S0142:1, S0344:1, UNKWN:1, L0369:1, L0762:1, L0371:1, L0796:1, L0761:1, L0373:1, L0773:1, L0521:1, L0794:1, L0804:1, L0784:1, L0518:1, L0783:1, L0647:1, L5622:1, L5623:1, L3391:1, L2657:1, L2262:1, L3636:1, H0144:1, H0684:1, H0659:1, H0658:1, S0330:1, S0152:1, H0696:1, S0404:1, S0037:1, L0746:1, L0779:1, S0031:1, H0707:1, S0434:1, L0480:1, L0608:1, L0604:1, S0011:1, S0192:1, S0456:1 and H0506:1.</p> <p>AR313:9, AR164:8, AR165:8, AR166:8, AR163:7, AR161:7, AR162:7, AR089:6, AR039:5, AR173:5, AR096:5, AR180:5, AR192:4, AR263:4, AR299:4, AR282:4, AR242:4, AR053:4, AR178:4, AR175:4, AR247:4, AR269:4, AR296:4, AR257:3, AR212:3, AR174:3, AR240:3, AR262:3, AR196:3, AR274:3, AR312:3, AR234:3, AR229:3, AR199:3, AR243:3, AR264:3, AR185:3, AR300:3, AR179:3, AR311:3, AR191:3, AR293:3, AR181:3, AR272:3, AR297:3, AR213:3, AR171:3, AR270:3, AR183:3, AR238:3, AR236:3, AR316:3, AR060:3, AR308:3, AR294:3, AR266:3, AR226:3, AR177:3, AR258:3, AR285:2, AR104:2, AR233:2, AR172:2, AR193:2, AR197:2, AR291:2, AR231:2, AR188:2, AR219:2, AR255:2, AR275:2, AR189:2, AR237:2, AR290:2, AR295:2, AR287:2, AR277:2, AR218:2, AR267:2, AR182:2, AR228:2, AR268:2, AR204:2, AR190:2, AR246:2, AR239:2, AR232:2, AR261:2, AR223:2, AR201:2, AR217:2, AR195:2, AR260:1, AR170:1, AR286:1, AR216:1, AR288:1, AR222:1, AR227:1, AR230:1 H0305:2 and H0589:1.</p>
44	HCWUM50	639037	54	<p>AR180:4, AR165:4, AR164:4, AR166:4, AR313:4, AR162:3, AR161:3, AR163:3, AR223:3, AR089:2, AR311:2, AR193:2, AR216:2, AR275:2, AR263:2, AR096:2, AR225:2, AR269:2, AR179:2, AR309:2, AR291:2, AR289:2, AR240:2, AR266:2, AR247:2, AR221:2, AR212:2, AR308:2, AR224:2, AR213:2, AR282:2, AR177:2, AR171:2, AR237:1, AR188:1, AR268:1, AR299:1, AR178:1, AR283:1, AR196:1, AR257:1, AR300:1, AR181:1, AR172:1, AR214:1, AR270:1, AR272:1, AR175:1, AR316:1 L0766:8, H0265:4, H0556:4, L0748:2, S0114:1, H0589:1, H0587:1, H0052:1, H0264:1, T0041:1, H0539:1 and H0187:1.</p>
45	HDABR72	1301517	55	<p>AR313:22, AR164:16, AR165:15, AR196:15, AR166:14, AR300:13, AR173:13, AR247:12, AR229:12, AR180:11, AR161:11, AR162:11, AR175:10, AR163:10, AR258:10, AR262:10, AR199:10, AR312:10, AR178:9, AR257:9, AR299:9, AR212:9, AR240:9, AR293:9, AR234:9, AR236:9, AR179:8, AR089:8, AR191:8, AR213:8, AR181:8, AR242:8, AR193:8, AR238:8, AR192:8, AR183:8, AR053:7, AR174:7, AR200:7, AR177:7, AR282:7, AR033:7, AR269:7, AR226:7, AR096:7, AR203:7, AR297:7, AR189:7, AR296:7, AR233:7, AR270:7, AR185:7, AR285:7, AR287:6, AR294:6, AR255:6, AR275:6, AR182:6, AR188:6, AR308:6, AR264:6, AR195:6, AR218:6, AR237:6, AR261:6, AR176:6, AR309:6, AR290:6, AR268:6, AR231:5, AR291:5, AR230:5, AR235:5, AR263:5, AR316:5,</p>

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46	HDPBA28	1062783	56	AR249:72, AR213:48, AR253:40, AR096:37, AR052:37, AR263:33, AR053:32, AR212:31, AR265:27, AR184:26, AR254:26, AR264:22, AR248:18, AR251:17, AR240:17, AR313:16, AR268:14, AR272:13, AR290:13, AR311:13, AR310:13, AR177:13, AR180:13, AR246:13, AR245:10, AR250:10, AR309:10, AR275:10, AR183:9, AR247:9, AR274:9, AR312:9, AR039:9, AR308:9, AR269:9, AR271:8, AR179:8, AR270:8, AR267:8, AR316:7, AR198:7, AR252:7, AR244:7, AR243:7, AR175:6, AR193:6, AR195:6, AR165:6, AR299:6, AR192:6, AR166:6, AR201:6, AR164:6, AR162:6, AR161:6, AR242:6, AR163:6, AR273:6, AR300:5, AR197:5, AR284:5, AR282:5, AR055:5, AR181:4, AR169:4, AR174:4, AR185:4, AR061:4, AR089:4, AR298:4, AR259:4, AR234:4, AR293:3, AR182:3, AR202:3, AR205:3, AR231:3, AR215:3, AR283:3, AR236:3, AR225:3, AR173:2, AR178:2, AR060:2, AR294:2, AR186:2, AR296:2, AR222:2, AR285:2, AR281:2, AR104:2, AR292:2, AR176:2, AR295:2, AR207:2, AR217:2, AR229:2, AR289:2, AR226:2, AR291:2, AR206:2, AR172:2, AR288:2, AR033:2, AR235:2, AR238:2, AR191:2, AR170:2, AR194:2, AR232:2, AR230:2, AR286:2, AR189:1, AR257:1, AR190:1, AR199:1, AR277:1, AR287:1, AR200:1, AR224:1, AR171:1, AR297:1, AR223:1, AR168:1, AR228:1, AR266:1, AR258:1, AR233:1, AR204:1, AR262:1, AR315:1, AR255:1, AR237:1, AR280:1 H0521:4, L0454:2, S0442:2, L0758:2, H0720:1, H0255:1, S0376:1, H0486:1, H0581:1, H0373:1, H0268:1, S0440:1, L0763:1, L0803:1, H0435:1, H0658:1, L3833:1, H0522:1, L0748:1, L0749:1, L0588:1 and H0543:1.
	HDPBA28	866429	278	
47	HDPB132	1352360	57	AR033:18, AR104:14, AR253:11, AR188:9, AR186:8, AR248:8, AR165:6, AR164:6, AR230:6, AR223:5, AR195:5, AR250:5, AR215:5, AR221:5, AR161:5, AR191:4, AR196:4, AR261:3, AR275:3, AR206:3, AR245:3, AR271:3, AR254:3, AR274:3, AR282:3, AR052:3, AR162:3, AR246:3, AR189:3, AR224:3, AR183:3, AR204:3, AR200:3, AR205:3, AR214:3, AR309:3, AR268:3, AR264:3, AR312:2, AR287:2, AR168:2, AR270:2, AR222:2, AR311:2, AR247:2, AR299:2, AR290:2, AR291:2, AR277:2, AR217:2, AR308:2, AR053:2, AR226:2, AR185:2, AR286:2, AR096:2, AR089:2, AR310:2, AR292:2, AR249:1, AR061:1, AR240:1, AR212:1, AR293:1, AR313:1, AR316:1, AR269:1, AR210:1, AR251:1, AR060:1, AR039:1, AR178:1, AR199:1, AR284:1, AR197:1, AR171:1 L0769:6, S0106:2, S0110:1, H0441:1, S0049:1, H0052:1, S0050:1, L0773:1, L0384:1, L0789:1, H0521:1, L0741:1, L0758:1 and L0366:1.
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	HDPB132	590733	280	
48	HDPCJ91	740748	58	AR274:86, AR216:79, AR214:77, AR205:65, AR222:63, AR245:61, AR246:60, AR215:59, AR223:59, AR224:58,

49	HDPCL63	1019008	59	<p>AR212:55, AR213:53, AR217:53, AR272:53, AR168:52, AR169:51, AR171:50, AR252:48, AR195:45, AR225:45, AR170:45, AR089:44, AR308:44, AR053:44, AR039:43, AR197:43, AR312:42, AR172:42, AR313:41, AR218:41, AR165:40, AR271:40, AR221:37, AR096:37, AR254:37, AR164:37, AR166:36, AR247:36, AR309:36, AR299:35, AR163:35, AR210:33, AR161:32, AR162:32, AR253:32, AR236:30, AR311:30, AR316:29, AR173:29, AR199:28, AR060:28, AR188:28, AR179:28, AR250:27, AR189:27, AR192:27, AR174:26, AR211:26, AR263:26, AR282:26, AR185:26, AR190:25, AR204:25, AR275:24, AR283:24, AR198:24, AR175:23, AR201:23, AR243:23, AR183:23, AR219:22, AR291:22, AR240:22, AR267:22, AR288:20, AR290:20, AR295:20, AR300:20, AR180:20, AR193:19, AR277:19, AR178:19, AR177:19, AR268:19, AR296:19, AR266:18, AR269:18, AR256:18, AR264:18, AR297:18, AR293:17, AR242:17, AR191:17, AR261:17, AR262:17, AR231:17, AR255:16, AR203:16, AR237:16, AR200:16, AR181:16, AR176:15, AR289:15, AR182:15, AR104:15, AR270:15, AR232:14, AR230:14, AR285:13, AR287:13, AR033:13, AR257:13, AR239:13, AR229:13, AR258:13, AR061:13, AR207:12, AR234:12, AR260:12, AR055:12, AR233:11, AR294:11, AR286:11, AR227:10, AR196:10, AR238:10, AR235:10, AR226:10, AR228:9, H0580:2, L0766:2, S0114:1, S0218:1, S0442:1, S0045:1, H0333:1, H0013:1, S0474:1, H0581:1, S0388:1, S6028:1, H0266:1, S0150:1, L0791:1, S0052:1, H0519:1, H0521:1, L0740:1 and L0754:1.</p> <p>AR281:19, AR202:15, AR194:15, AR196:14, AR315:13, AR207:13, AR206:13, AR265:13, AR205:12, AR244:12, AR195:12, AR222:11, AR033:11, AR235:10, AR214:10, AR263:10, AR225:10, AR218:10, AR246:10, AR197:10, AR261:10, AR284:10, AR310:10, AR170:10, AR242:10, AR224:10, AR198:10, AR162:10, AR311:9, AR161:9, AR172:9, AR192:9, AR241:9, AR169:9, AR223:9, AR171:9, AR291:9, AR183:9, AR314:9, AR273:9, AR215:9, AR163:9, AR298:9, AR216:8, AR295:8, AR217:8, AR174:8, AR240:8, AR280:8, AR282:8, AR275:8, AR193:8, AR181:8, AR243:8, AR245:8, AR252:8, AR221:8, AR168:8, AR264:8, AR219:8, AR285:8, AR271:8, AR165:7, AR176:7, AR177:7, AR201:7, AR296:7, AR211:7, AR191:7, AR270:7, AR212:7, AR175:7, AR164:7, AR269:7, AR247:7, AR184:7, AR289:7, AR288:7, AR309:7, AR286:7, AR210:7, AR213:7, AR268:7, AR250:7, AR200:7, AR287:7, AR189:7, AR292:7, AR053:7, AR266:7, AR104:6, AR173:6, AR204:6, AR297:6, AR283:6, AR272:6, AR290:6, AR236:6, AR182:6, AR312:6, AR308:6, AR180:6, AR096:6, AR277:6, AR188:6, AR293:6, AR186:6, AR299:6, AR190:5, AR052:5, AR300:5, AR199:5, AR039:5, AR251:5, AR089:5, AR249:5, AR178:5, AR231:5, AR294:5, AR248:5, AR274:5, AR316:5, AR055:4, AR232:4, AR257:4, AR267:4, AR313:4, AR262:4, AR258:4, AR234:4, AR238:4, AR229:4, AR203:4, AR254:4, AR256:3, AR061:3, AR255:3, AR179:3, AR226:3, AR185:3, AR259:3, AR227:3, AR260:3, AR230:3, AR060:3, AR239:3, AR233:3, AR237:3, AR253:2, AR228:2, L0751:8, L0439:6, L0659:5, L0438:4, L0744:4, L0774:4, S0046:3, H0052:3, H0009:3, H0271:3, L0662:3, L0665:3, L0747:3, H0740:2, S0358:2, H0586:2, H0251:2, H0100:2, L3905:2, L0794:2, L0803:2, L0809:2, H0519:2, S0126:2, L0749:2, L0731:2, L0757:2, L0605:2, H0170:1, H0717:1, H0295:1, L0294:1, L0785:1, S0116:1, H0483:1, L3659:1, S0418:1, H0742:1, H0735:1, S0045:1, H0619:1, H0550:1, H0370:1, H0592:1, H0574:1, H0427:1, H0599:1, T0082:1, S0010:1, S0049:1, H0544:1, H0545:1, H0570:1, H0051:1, S0388:1, H0356:1, H0399:1, H0266:1, H0622:1, L0194:1, H0135:1, H0412:1, H0623:1, H0059:1, L0351:1, T0042:1, H0561:1, S0294:1, L0640:1, L4747:1, L5575:1, L5565:1, L0800:1, L0764:1, L0648:1, L0768:1, L0774:1, L0776:1, L0657:1, L0559:1, L0519:1, L0789:1, L0792:1, L0666:1, L0664:1, L0709:1, L3811:1, H0520:1, H0547:1, S0328:1, S0378:1, H0754:1, S0152:1, H0521:1, S0190:1, S0406:1,</p>
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	HDPCL63	897484		282	
50	HDPCT05	460682		60	AR060:2, AR055:2, AR282:2, H0521:2, H0445:2, H0394:1, H0747:1, H0581:1, L0761:1 and L0750:1.
51	HDPCT01	771583		61	AR268:5, AR244:4, AR282:3, AR251:3, AR242:3, AR241:3, AR052:3, AR184:2, AR271:2, AR310:2, AR176:2, AR194:2, AR039:2, AR309:2, AR283:1, AR178:1, AR289:1, AR217:1, AR257:1, AR277:1, AR170:1, AR284:1, AR221:1, AR226:1, AR265:1, H0521:3, S0278:2, S0222:2, H0284:2, H0265:1, H0728:1, S0007:1, H0208:1, H0586:1, H0497:1, H0642:1, H0581:1, H0052:1, H0572:1, H0024:1, H0292:1, H0428:1, H0628:1, H0135:1, H0163:1, H0433:1, S0002:1, L2263:1, L0438:1, L3829:1, H0539:1, S0027:1, S0032:1, L0439:1, S0436:1, S0458:1 and H0352:1.
52	HDPHI51	460679		62	AR195:9, AR192:9, AR207:9, AR215:8, AR264:8, AR225:7, AR263:7, AR311:7, AR168:7, AR309:7, AR252:6, AR172:6, AR245:6, AR161:6, AR162:6, AR163:6, AR196:6, AR223:6, AR193:6, AR177:6, AR246:6, AR224:6, AR197:5, AR308:5, AR272:5, AR214:5, AR275:5, AR222:5, AR253:5, AR176:5, AR261:5, AR295:5, AR291:5, AR171:5, AR218:5, AR221:5, AR219:5, AR188:5, AR165:5, AR096:5, AR217:5, AR238:5, AR288:5, AR164:5, AR175:5, AR166:5, AR089:5, AR271:5, AR060:4, AR240:4, AR183:4, AR201:4, AR257:4, AR169:4, AR312:4, AR316:4, AR039:4, AR274:4, AR190:4, AR191:4, AR181:4, AR178:4, AR236:4, AR216:4, AR180:4, AR205:4, AR210:4, AR270:4, AR170:4, AR277:4, AR243:4, AR235:4, AR212:4, AR104:4, AR199:4, AR189:4, AR242:4, AR213:4, AR255:4, AR289:4, AR174:3, AR285:3, AR230:3, AR286:3, AR297:3, AR299:3, AR283:3, AR313:3, AR204:3, AR287:3, AR173:3, AR247:3, AR229:3, AR269:3, AR296:3, AR182:3, AR293:3, AR266:3, AR258:3, AR198:3, AR237:3, AR262:3, AR033:3, AR239:3, AR185:3, AR231:3, AR203:3, AR200:3, AR179:3, AR211:3, AR227:3, AR268:3, AR267:3, AR294:3, AR290:3, AR234:3, AR232:3, AR226:3, AR300:2, AR250:2, AR282:2, AR256:2, AR061:2, AR053:2, AR233:2, AR260:2, AR228:2, AR055:2, H0521:1.
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54	HDPND46	637586		64	AR252:7, AR170:6, AR223:6, AR207:6, AR311:6, AR165:6, AR263:5, AR162:5, AR163:5, AR164:5, AR214:5,

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57	HDPPN86	895711	284	<p>AR197:9, AR060:8, AR253:8, AR161:8, AR162:8, AR163:8, AR165:8, AR164:7, AR089:7, AR166:7, AR204:7, AR192:7, AR207:7, AR177:6, AR193:6, AR185:6, AR235:6, AR271:6, AR195:6, AR053:6, AR312:6, AR233:6, AR232:6, AR174:5, AR282:5, AR104:5, AR299:5, AR227:5, AR181:5, AR125:5, AR309:5, AR264:5, AR205:5, AR308:5, AR178:5, AR237:5, AR061:5, AR313:5, AR300:5, AR175:5, AR263:5, AR247:5, AR223:5, AR173:5, AR226:5, AR272:5, AR243:5, AR240:5, AR311:5, AR055:5, AR269:5, AR201:4, AR229:4, AR286:4, AR182:4, AR246:4, AR236:4, AR295:4, AR316:4, AR285:4, AR261:4, AR293:4, AR275:4, AR291:4, AR228:4, AR274:4, AR296:4, AR176:4, AR213:4, AR297:4, AR179:4, AR270:4, AR254:4, AR039:4, AR239:4, AR262:4, AR288:4, AR180:4, AR287:4, AR096:4, AR238:4, AR183:4, AR203:4, AR033:4, AR257:4, AR234:4, AR230:4, AR294:3, AR198:3, AR289:3, AR255:3, AR266:3, AR258:3, AR267:3, AR283:3, AR168:3, AR217:3, AR231:3, AR214:3, AR277:3, AR252:3, AR196:3, AR250:3, AR218:3, AR245:3, AR190:2, AR216:2, AR268:2, AR224:2, AR290:2, AR188:2, AR191:2, AR189:2, AR221:2, AR260:2, AR222:2, AR200:2, AR171:2, AR211:2, AR210:2, AR219:2, AR172:2, AR199:2, AR215:1, AR170:1, AR225:1, AR256:1, L0769:5, L0774:3, H0656:2, S0442:2, S0358:2, S0360:2, S0278:2, H0620:2, L0500:2, L0775:2, L0710:2, L0777:2, L0752:2, L0588:2, H0149:1, H0295:1, T0049:1, H0381:1, H0484:1, H0483:1, H0638:1, S0420:1, S0444:1, S0408:1, S0045:1, H0587:1, H0318:1, H0204:1, H0530:1, H0545:1, H0178:1, L0471:1, L0142:1, H0181:1, H0087:1, H0412:1, H0623:1, H0100:1, S0438:1, H0633:1, H0646:1, H0529:1, L0506:1, L0761:1, L0764:1, L0648:1, L0766:1, L0497:1, L0493:1, L0511:1, L0665:1, L2260:1, H0698:1, H0690:1, H0521:1, S0406:1, S3014:1, L0747:1, L0780:1, H0543:1 and H0422:1.</p>
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	HDPSB18	905414	286	
58	HDPSB18	732097	287	<p>AR214:47, AR207:47, AR263:40, AR222:34, AR169:33, AR235:33, AR212:31, AR213:30, AR223:29, AR170:29, AR311:29, AR309:28, AR168:28, AR195:27, AR264:26, AR192:26, AR224:26, AR216:24, AR295:24, AR171:24, AR245:24, AR217:23, AR172:23, AR198:22, AR308:22, AR271:22, AR161:21, AR162:21, AR163:21, AR252:21, AR261:21, AR288:21, AR053:20, AR166:20, AR197:20, AR242:20, AR201:20, AR033:19, AR205:19, AR177:19, AR312:19, AR193:19, AR165:18, AR240:18, AR229:18, AR277:18, AR254:18, AR164:18, AR225:17, AR246:17, AR297:17, AR236:17, AR285:16, AR291:16, AR275:16, AR238:16, AR272:16, AR174:15, AR296:15, AR274:15, AR232:15, AR286:14, AR282:14, AR230:13, AR181:13, AR211:13, AR250:13, AR226:13, AR239:13, AR287:12, AR227:12, AR283:12, AR247:12, AR237:12, AR289:12, AR215:12, AR316:12, AR204:12, AR210:12, AR176:12, AR180:12, AR293:12, AR231:11, AR270:11, AR300:11, AR299:11, AR262:11, AR175:11, AR185:11, AR243:11, AR196:11, AR221:11, AR258:10, AR269:10, AR200:10, AR313:10, AR089:10, AR253:10, AR183:10, AR294:10, AR268:9, AR061:9, AR104:9, AR173:9, AR234:9, AR199:9, AR096:9, AR179:9, AR218:8, AR178:8, AR233:8, AR257:8, AR219:8, AR255:8, AR266:8, AR290:8, AR267:8, AR188:8, AR228:8, AR189:7, AR055:7, AR060:7, AR203:7, AR191:7, AR256:7, AR039:7, AR260:6, AR182:6, AR190:6, L0804:2, H0521:2, L0021:1, H0617:1, H0623:1, L0648:1 and L0665:1.</p>
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	HDPHSH53	1040056	288	
	HDPHSH53	882768	289	
59	HDPSP01	1352280	69	AR169:8, AR235:5, AR265:5, AR180:4, AR176:4, AR161:4, AR163:4, AR311:4, AR162:4, AR269:3, AR165:3, AR172:3, AR171:3, AR222:3, AR166:3, AR183:3, AR225:3, AR168:3, AR282:3, AR224:3, AR245:3, AR272:3, AR196:3, AR223:3, AR297:3, AR221:2, AR182:2, AR298:2, AR164:2, AR261:2, AR257:2, AR170:2, AR270:2, AR289:2, AR216:2, AR173:2, AR191:2, AR214:2, AR287:2, AR296:2, AR242:2, AR228:2, AR247:2, AR295:2, AR255:2, AR192:2, AR240:2, AR174:2, AR227:2, AR053:2, AR275:2, AR203:2, AR266:2, AR288:2, AR215:2, AR277:2, AR239:2, AR291:2, AR264:2, AR263:2, AR285:2, AR230:2, AR190:2, AR310:2, AR189:2, AR274:1, AR181:1, AR286:1, AR179:1, AR226:1, AR246:1, AR231:1, AR178:1, AR175:1, AR238:1, AR233:1, AR273:1, AR290:1, AR243:1, AR200:1, AR293:1, AR294:1, AR309:1, AR284:1, AR312:1, AR313:1, AR234:1, AR229:1, AR061:1, AR300:1, AR217:1, AR268:1, AR292:1, AR089:1, AR262:1 L0769:6, L0751:5, L0752:5, H0617:4, L0806:4, L0731:4, L0771:3, L0774:3, H0370:2, S0314:2, H0551:2, H0059:2, L0792:2, L0745:2, L0750:2, L0777:2, S0444:1, H0728:1, S0132:1, H0550:1, H0392:1, H0586:1, H0427:1, H0618:1, H0052:1, H0545:1, H0123:1, H0620:1, S0051:1, H0135:1, H0100:1, H0494:1, L0800:1, L0764:1, L0804:1, L0775:1, L0805:1, L0783:1, L0809:1, L0666:1, L0665:1, H0684:1, S0328:1, H0521:1, H0555:1, H0478:1, L0743:1, L0747:1, L0779:1, L0780:1, L0755:1 and S0434:1.
60	HDPSP01	689129	290	
	HDPSP54	744440	70	AR263:53, AR207:53, AR214:51, AR169:41, AR224:40, AR222:38, AR223:37, AR195:36, AR235:32, AR217:31, AR212:31, AR168:30, AR172:30, AR311:29, AR053:28, AR192:28, AR196:28, AR171:27, AR198:27, AR213:27, AR221:27, AR161:26, AR264:26, AR252:26, AR162:25, AR170:25, AR210:25, AR245:24, AR033:23, AR225:23, AR216:23, AR163:22, AR089:22, AR261:22, AR215:21, AR271:21, AR177:21, AR181:21, AR104:21, AR295:20, AR218:20, AR236:19, AR193:19, AR191:19, AR211:19, AR197:18, AR185:18, AR055:18, AR219:18, AR201:18, AR240:18, AR165:17, AR316:17, AR299:17, AR164:17, AR060:17, AR253:17, AR174:16, AR242:16, AR288:16, AR199:16, AR205:16, AR246:15, AR282:15, AR039:15, AR238:15, AR308:15, AR229:15, AR175:14, AR188:14, AR285:14, AR297:14, AR254:14, AR189:14, AR232:14, AR277:13, AR300:13, AR287:13, AR243:13, AR230:13, AR312:13, AR291:13, AR286:12, AR204:12, AR250:12, AR226:12, AR173:12, AR200:12, AR239:12, AR176:12, AR274:11, AR296:11, AR309:11, AR203:11, AR231:11, AR270:11, AR247:11, AR293:11, AR190:11, AR283:10, AR258:10, AR267:10, AR234:10, AR289:10, AR262:10, AR178:10, AR268:10, AR227:10, AR313:10, AR180:10, AR237:10, AR179:9, AR257:9, AR182:9, AR269:9, AR255:9, AR233:9, AR260:9, AR061:9, AR183:9, AR290:8, AR275:8, AR272:8, AR266:8, AR294:7, AR256:7, AR228:6 L0740:8, L0662:3, L0659:3, L0663:3, S0422:2, L0646:2, L0766:2, L0439:2, L0779:2, H0171:1, S6024:1, S0110:1, S0360:1, H0411:1, H0455:1, S0474:1, H0510:1, S0438:1, L0637:1, L5565:1, L0771:1, L0773:1, L0794:1, L0804:1, L0787:1, L0665:1, L0438:1, H0521:1, S0406:1, L0754:1, L0755:1 and L0758:1.
61	HDPSP54	502472	291	
	HDPUPH26	866433	71	AR177:16, AR176:15, AR174:15, AR175:14, AR235:13, AR273:12, AR183:12, AR191:11, AR251:11, AR261:11, AR182:10, AR170:10, AR310:9, AR190:9, AR171:9, AR189:9, AR169:9, AR173:9, AR195:9, AR214:8, AR224:8,

62	HDPWU68	812737	72	<p>AR265:8, AR215:8, AR297:8, AR222:7, AR197:7, AR243:7, AR269:7, AR221:7, AR288:7, AR165:7, AR217:7, AR285:7, AR188:7, AR202:7, AR164:7, AR263:7, AR216:7, AR287:7, AR161:7, AR162:7, AR291:7, AR168:7, AR172:6, AR163:6, AR166:6, AR270:6, AR292:6, AR223:6, AR180:6, AR295:6, AR284:6, AR245:6, AR053:6, AR207:6, AR315:6, AR271:6, AR298:5, AR268:5, AR196:5, AR255:5, AR311:5, AR194:5, AR211:5, AR201:5, AR236:5, AR226:5, AR264:5, AR238:5, AR312:5, AR198:5, AR232:5, AR181:5, AR262:4, AR257:4, AR178:4, AR249:4, AR282:4, AR213:4, AR199:4, AR206:4, AR252:4, AR192:4, AR247:4, AR193:4, AR308:4, AR239:4, AR205:4, AR212:4, AR274:4, AR203:4, AR225:4, AR272:4, AR242:4, AR309:4, AR266:4, AR286:4, AR296:4, AR289:3, AR267:3, AR234:3, AR185:3, AR240:3, AR237:3, AR231:3, AR227:3, AR250:3, AR299:3, AR089:3, AR210:3, AR033:3, AR248:3, AR314:3, AR293:3, AR246:3, AR290:3, AR294:3, AR060:3, AR316:3, AR230:3, AR039:3, AR258:3, AR280:3, AR275:3, AR200:3, AR233:3, AR229:3, AR283:2, AR061:2, AR253:2, AR277:2, AR313:2, AR228:2, AR281:2, AR300:2, AR096:2, AR179:2, AR256:2, AR260:2, AR104:2, AR219:2, AR244:2, AR204:2, AR186:1, AR218:1, AR052:1, AR259:1, AR055:1, S0358:4, S0280:3, H0717:2, H0370:2, H0510:2, H0556:1, H0716:1, S0442:1, S0354:1, S0476:1, H0393:1, H0549:1, H0586:1, T0082:1, H0036:1, H0590:1, H0596:1, H0050:1, H0628:1, H0264:1, H0494:1, H0509:1, L2257:1, L2654:1, H0521:1, L0741:1, L0439:1, H0445:1, S0436:1, L0605:1, S0011:1 and H0665:1.</p>
63	HDPWU34	630354	73	<p>AR253:15, AR052:14, AR213:11, AR184:11, AR230:11, AR228:9, AR170:9, AR250:8, AR168:8, AR254:8, AR225:6, AR297:6, AR053:6, AR251:5, AR267:5, AR248:5, AR268:5, AR221:5, AR096:5, AR214:5, AR238:5, AR178:5, AR249:5, AR216:5, AR173:5, AR239:5, AR236:5, AR166:5, AR182:4, AR161:4, AR162:4, AR217:4, AR269:4, AR282:4, AR163:4, AR224:4, AR222:4, AR237:4, AR296:4, AR257:4, AR263:4, AR244:4, AR227:4, AR258:4, AR252:4, AR291:4, AR229:4, AR219:4, AR287:4, AR290:4, AR275:4, AR264:4, AR183:4, AR175:4, AR223:4, AR199:4, AR308:4, AR171:3, AR194:3, AR246:3, AR277:3, AR260:3, AR288:3, AR240:3, AR274:3, AR191:3, AR284:3, AR243:3, AR312:3, AR293:3, AR179:3, AR233:3, AR300:3, AR261:3, AR218:3, AR165:3, AR061:3, AR231:3, AR033:3, AR298:3, AR316:3, AR164:3, AR181:3, AR255:3, AR270:3, AR189:3, AR313:3, AR309:3, AR234:2, AR186:2, AR247:2, AR195:2, AR285:2, AR232:2, AR292:2, AR185:2, AR226:2, AR180:2, AR299:2, AR289:2, AR271:2, AR193:2, AR089:2, AR203:2, AR311:2, AR060:2, AR172:2, AR310:2, AR215:2, AR177:2, AR266:2, AR262:2, AR272:2, AR188:2, AR196:2, AR169:1, AR212:1, AR210:1, AR055:1, AR283:1, AR190:1, AR241:1, AR295:1, AR286:1, AR201:1, AR294:1, AR104:1, AR256:1, AR205:1, AR039:1, H0677:47, H0521:14, H0295:3, H0587:3, H0556:2, H0656:2, H0638:2, H0411:2, S0002:2, L0766:2, L0776:2, L0659:2, L0809:2, H0670:2, H0522:2, S0404:2, L0743:2, L0744:2, L0740:2, L0731:2, S0134:1, H0657:1, H0254:1, S0476:1, S0278:1, H0486:1, H0575:1, H0606:1, H0135:1, H0561:1, S0438:1, L0761:1, L0768:1, L0655:1, L2261:1, S0374:1, H0690:1, H0435:1, H0658:1, H0696:1, H0678:1, L0779:1, L0752:1, H0445:1, S0434:1 and S0436:1.</p>

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	HDPWU34	701979	292	
64	HDPXY01	879048	74	AR207:8, AR165:8, AR245:8, AR214:8, AR164:8, AR275:8, AR163:8, AR162:8, AR263:8, AR169:8, AR195:7, AR166:7, AR274:7, AR161:7, AR309:7, AR272:7, AR170:7, AR212:7, AR308:6, AR311:6, AR198:6, AR089:6, AR060:6, AR197:6, AR192:6, AR264:6, AR039:6, AR177:6, AR243:6, AR223:6, AR235:5, AR213:5, AR096:5, AR282:5, AR168:5, AR313:5, AR222:5, AR240:5, AR204:5, AR217:5, AR261:5, AR193:4, AR312:4, AR104:4, AR224:4, AR246:4, AR176:4, AR055:4, AR299:4, AR171:4, AR283:4, AR271:4, AR277:4, AR174:4, AR316:4, AR178:4, AR295:4, AR053:4, AR205:4, AR185:4, AR237:4, AR033:4, AR247:4, AR300:4, AR266:4, AR257:3, AR270:3, AR181:3, AR293:3, AR233:3, AR250:3, AR225:3, AR288:3, AR291:3, AR216:3, AR296:3, AR201:3, AR286:3, AR285:3, AR268:3, AR228:3, AR297:3, AR254:3, AR294:3, AR252:3, AR269:3, AR229:3, AR287:3, AR232:3, AR061:3, AR234:3, AR289:3, AR183:3, AR227:3, AR231:3, AR211:3, AR267:3, AR230:3, AR255:3, AR236:3, AR239:2, AR226:2, AR179:2, AR200:2, AR182:2, AR262:2, AR175:2, AR203:2, AR180:2, AR290:2, AR196:2, AR199:2, AR189:2, AR258:2, AR173:2, AR210:2, AR191:2, AR238:1, AR190:1, AR253:1, AR215:1, AR172:1, L0646:4, L0666:4, L0662:3, L0749:3, H0661:2, H0620:2, H0617:2, H0144:2, L0777:2, L0731:2, H0170:1, S0360:1, S0046:1, L0717:1, H0013:1, H0052:1, H0039:1, H0622:1, H0606:1, H0673:1, L0769:1, L0796:1, L5565:1, L5566:1, L0764:1, L0648:1, L0381:1, L0805:1, L0659:1, L0789:1, L0792:1, L0663:1, L0665:1, H0689:1, H0660:1, H0648:1, H0539:1, H0521:1, L0779:1 and L0603:1.
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	HDPXY01	895716	294	
	HDPXY01	895715	295	
65	HDTBV77	785879	75	AR183:7, AR184:5, AR269:4, AR207:4, AR245:4, AR270:4, AR182:4, AR214:4, AR172:4, AR223:4, AR263:3, AR272:3, AR180:3, AR176:3, AR268:3, AR309:3, AR175:3, AR164:3, AR282:3, AR166:3, AR222:3, AR225:3, AR216:3, AR308:3, AR052:3, AR247:3, AR289:3, AR165:3, AR266:2, AR312:2, AR162:2, AR169:2, AR291:2,

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66	HDTDQ23	1306984	76	AR200:16, AR311:15, AR272:13, AR264:12, AR165:11, AR164:11, AR188:11, AR312:10, AR166:10, AR211:10, AR104:10, AR282:10, AR191:10, AR246:9, AR096:9, AR210:9, AR189:9, AR162:9, AR199:9, AR161:9, AR163:9, AR274:9, AR196:9, AR308:8, AR174:8, AR089:8, AR240:8, AR309:7, AR175:7, AR218:7, AR219:7, AR190:7, AR295:7, AR203:7, AR316:7, AR299:7, AR313:6, AR285:6, AR247:6, AR185:6, AR275:6, AR263:6, AR183:6, AR245:6, AR060:6, AR181:6, AR212:6, AR039:6, AR053:5, AR288:5, AR269:5, AR268:5, AR243:5, AR291:5, AR290:5, AR033:5, AR173:5, AR238:5, AR267:5, AR231:5, AR176:5, AR271:5, AR300:4, AR237:4, AR205:4, AR266:4, AR177:4, AR182:4, AR223:4, AR270:4, AR296:4, AR213:4, AR277:4, AR229:4, AR178:4, AR261:4, AR171:4, AR297:3, AR195:3, AR287:3, AR239:3, AR232:3, AR230:3, AR255:3, AR234:3, AR226:3, AR257:3, AR286:3, AR293:3, AR258:3, AR236:3, AR193:3, AR262:3, AR168:3, AR180:3, AR252:3, AR289:3, AR221:3, AR225:3, AR250:3, AR179:3, AR294:3, AR216:2, AR201:2, AR198:2, AR233:2, AR061:2, AR172:2, AR222:2, AR055:2, AR170:2, AR215:2, AR256:2, AR228:2, AR272:2, AR224:2, AR214:1, AR283:1, AR197:1, AR260:1, AR235:1, AR253:1 L0659:5, L0666:4, L0665:4, L2634:3, L0471:2, H0031:2, L0646:2, L0794:2, L0766:2, L0657:2, H0265:1, H0685:1, L0785:1, S0356:1, S0376:1, S0360:1, H0742:1, S0007:1, H0747:1, H0486:1, L2540:1, H0069:1, H0025:1, H0457:1, H0252:1, H0428:1, L0055:1, H0038:1, S0344:1, L0625:1, L0761:1, L0800:1, L0553:1, L0649:1, L0803:1, L0650:1, L0606:1, L3872:1, L0791:1, L0663:1, L0664:1, H0684:1, H0435:1, H0648:1, S0380:1, L3832:1, L0749:1, L0786:1, L0780:1, L0755:1, L0759:1, L0596:1, L0601:1, H0543:1 and H0422:1.
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	HDTDQ23	751707	297	
67	HE2DE47	619852	77	AR224:15, AR223:15, AR217:12, AR214:12, AR222:11, AR225:11, AR172:9, AR216:9, AR215:9, AR221:8, AR171:7, AR162:7, AR168:7, AR161:7, AR264:7, AR196:7, AR176:6, AR163:6, AR165:6, AR263:6, AR246:6, AR164:6, AR309:6, AR166:6, AR193:6, AR170:6, AR313:5, AR096:5, AR089:5, AR250:5, AR169:5, AR242:5, AR312:5, AR261:5, AR254:5, AR295:5, AR245:5, AR180:5, AR189:5, AR271:5, AR191:5, AR291:5, AR274:5, AR177:5, AR316:4, AR178:4, AR201:4, AR272:4, AR253:4, AR183:4, AR267:4, AR308:4, AR270:4, AR282:4, AR229:4, AR174:4, AR175:4, AR188:4, AR268:4, AR190:4, AR288:4, AR183:4, AR060:4, AR297:4, AR181:4, AR192:4, AR173:4, AR255:4, AR195:4, AR296:4, AR179:4, AR285:4, AR311:4, AR199:4, AR197:4, AR205:4, AR231:4, AR237:4, AR243:4, AR239:4, AR299:4, AR300:3, AR236:3, AR182:3, AR257:3, AR212:3, AR269:3, AR218:3, AR290:3, AR238:3, AR275:3, AR262:3, AR203:3, AR198:3, AR266:3, AR053:3, AR287:3, AR210:3, AR228:3, AR293:3,

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83	HFIIN69	1011487	93	AR239:7, AR223:4, AR225:4, AR216:4, AR221:3, AR235:3, AR266:3, AR282:3, AR243:2, AR215:2, AR240:2, AR089:2, AR277:2, AR039:1, AR247:1, AR224:1, AR261:1, AR264:1, AR162:1, AR161:1, AR163:1, AR175:1, AR179:1, AR291:1, AR171:1, AR195:1, AR230:1 S0222:1, S0152:1, L0759:1 and S0194:1.
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	HFIIN69	874248	303	

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85	HFKFG02	634743	95	AR264:12, AR309:11, AR252:11, AR225:11, AR271:10, AR214:10, AR272:10, AR161:10, AR275:9, AR162:9, AR216:9, AR053:9, AR215:9, AR197:9, AR163:9, AR311:9, AR223:9, AR263:8, AR308:8, AR207:8, AR195:8, AR169:8, AR217:8, AR172:8, AR291:8, AR246:8, AR060:7, AR171:7, AR196:7, AR245:7, AR182:7, AR224:7, AR274:7, AR235:7, AR243:7, AR266:7, AR200:6, AR201:6, AR212:6, AR198:6, AR168:6, AR221:6, AR210:6, AR176:6, AR312:6, AR192:6, AR254:6, AR211:6, AR282:6, AR199:6, AR205:5, AR269:5, AR289:5, AR181:5, AR222:5, AR261:5, AR177:5, AR188:5, AR240:5, AR183:5, AR164:5, AR166:5, AR165:5, AR267:5, AR290:5, AR213:5, AR285:5, AR247:5, AR193:5, AR288:5, AR297:5, AR287:4, AR295:4, AR255:4, AR174:4, AR257:4, AR236:4, AR231:4, AR262:4, AR286:4, AR180:4, AR293:4, AR277:4, AR178:4, AR191:4, AR189:4, AR270:4, AR033:4, AR175:4, AR229:4, AR268:4, AR228:4, AR239:3, AR299:3, AR061:3, AR300:3, AR238:3, AR250:3, AR316:3, AR242:3, AR203:3, AR190:3, AR173:3, AR237:3, AR233:3, AR179:3, AR089:3, AR294:3, AR185:3, AR296:3, AR234:3, AR230:3, AR219:3, AR204:3, AR258:3, AR218:3, AR226:3, AR096:3, AR256:2, AR283:2, AR232:2, AR104:2, AR313:2, AR039:2, AR227:2, AR055:2, AR260:2, AR170:1 L0803:5, L0439:2, H0431:1, H0012:1, T0010:1, H0063:1 and L0774:1.
86	HFTBM50	545012	96	AR300:4, AR104:4, AR240:4, AR277:3, AR185:3, AR060:3, AR277:2, AR299:2, AR316:2, AR282:2, AR219:2, AR089:2, AR283:2, AR218:2, AR096:2, AR039:2, AR313:1 L0439:6, L0731:4, L0769:2, L0666:2, S0432:2, S0206:2, L0751:2, L0777:2, L0759:2, L0591:2, H0341:1, H0661:1, S0408:1, H0601:1, H0497:1, H0123:1, L0471:1, H0051:1, H0252:1, H0673:1, H0616:1, H0551:1, H0646:1, S0422:1, L0372:1, L0771:1, L0773:1, L0768:1, L0775:1, L0375:1, L0527:1, L0664:1, L0665:1, S0374:1, H0519:1, H0659:1, H0521:1, H0522:1, L0747:1, L0749:1, L0755:1, L0758:1, S0031:1, L0683:1, L0590:1 and L0595:1.
87	HFTDZ36	545726	97	AR282:5, AR176:3, AR252:2, AR270:2, AR287:2, AR309:2, AR221:2, AR263:2, AR291:2, AR224:2, AR233:2, AR181:2, AR198:2, AR240:2, AR222:2, AR193:2, AR214:2, AR286:2, AR165:2, AR164:1, AR178:1, AR236:1, AR201:1, AR168:1, AR089:1, AR262:1, AR060:1, AR217:1, AR161:1, AR272:1, AR264:1, AR061:1, AR195:1, AR257:1, AR268:1, AR215:1, AR285:1, AR258:1, AR210:1, AR104:1, AR196:1 L0779:5, L0758:4, S0036:2, H0038:2, S0422:2, L0662:2, L0803:2, H0171:1, H0208:1, H0411:1, S0222:1, H0013:1, H0108:1, H0581:1, H0123:1, H0024:1, H0373:1, S0051:1, S6028:1, H0615:1, L0794:1, L0804:1, S0126:1, H0436:1, S0028:1, L0756:1, L0777:1, L0731:1 and S0242:1.
88	HFXBL33	778070	98	AR163:25, AR161:24, AR162:24, AR313:23, AR173:17, AR180:17, AR196:17, AR165:17, AR166:16, AR229:16, AR164:16, AR270:14, AR247:14, AR182:14, AR238:14, AR234:14, AR175:14, AR179:13, AR269:13, AR181:13, AR178:13, AR199:12, AR258:12, AR262:12, AR240:11, AR233:11, AR257:11, AR183:11, AR264:11, AR300:10,

89	HFXHK73	609826	99	AR268:10, AR285:10, AR293:10, AR274:10, AR231:10, AR275:10, AR191:10, AR230:10, AR228:10, AR236:10, AR237:10, AR226:10, AR239:9, AR287:9, AR203:9, AR294:9, AR174:9, AR296:9, AR260:8, AR176:8, AR189:8, AR200:8, AR312:8, AR033:8, AR096:8, AR185:8, AR299:8, AR255:7, AR297:7, AR267:7, AR188:7, AR177:7, AR290:7, AR277:6, AR218:6, AR190:6, AR286:6, AR291:6, AR089:6, AR266:6, AR060:6, AR227:6, AR219:6, AR263:5, AR295:5, AR316:5, AR311:5, AR261:5, AR055:5, AR235:5, AR309:5, AR282:5, AR272:4, AR288:4, AR308:4, AR256:4, AR053:4, AR289:4, AR104:4, AR283:4, AR215:4, AR223:4, AR232:4, AR212:4, AR213:3, AR061:3, AR211:3, AR217:3, AR216:3, AR169:3, AR210:3, AR195:3, AR168:2, AR225:2, AR201:2, AR193:2, AR171:2, AR214:2, AR039:2, AR243:2, AR222:2, AR170:1, AR246:1, AR224:1 H0657:3, H0645:2, L0748:2, H0542:2, H0583:1, H0650:1, S0001:1, L0586:1, H0013:1, L0021:1, T0071:1, H0354:1, H0179:1, T0006:1, H0591:1, H0272:1, L0667:1, H0547:1, H0521:1, S0404:1, S0031:1 and L0599:1.
90	HFXJX44	701988	100	AR161:5, AR162:5, AR163:5, AR263:4, AR275:3, AR269:3, AR235:3, AR266:3, AR181:3, AR178:3, AR165:3, AR299:3, AR215:3, AR291:3, AR213:3, AR164:3, AR176:3, AR166:3, AR309:3, AR221:3, AR193:3, AR182:3, AR179:2, AR264:2, AR257:2, AR242:2, AR289:2, AR060:2, AR277:2, AR089:2, AR267:2, AR233:2, AR236:2, AR262:2, AR222:2, AR285:2, AR223:2, AR183:2, AR286:2, AR191:2, AR261:2, AR268:2, AR228:2, AR213:2, AR271:2, AR096:2, AR104:2, AR201:2, AR293:2, AR246:2, AR238:2, AR294:2, AR308:2, AR288:2, AR231:2, AR174:2, AR282:2, AR173:2, AR229:2, AR247:2, AR316:2, AR175:2, AR061:2, AR185:2, AR240:2, AR274:2, AR255:2, AR225:2, AR239:2, AR270:1, AR287:1, AR237:1, AR290:1, AR296:1, AR055:1, AR216:1, AR227:1, AR200:1, AR189:1, AR199:1, AR312:1, AR300:1, AR230:1, AR283:1, AR210:1, AR188:1, AR272:1, AR311:1 S0001:1
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93	HGLAF75	566838	103	AR196:8, AR191:7, AR269:7, AR215:7, AR180:6, AR188:6, AR270:6, AR223:6, AR173:6, AR198:5, AR176:5, AR178:5, AR268:5, AR055:5, AR165:5, AR175:5, AR181:5, AR266:5, AR161:5, AR162:5, AR264:5, AR183:5, AR060:5, AR174:5, AR164:5, AR291:5, AR163:5, AR172:5, AR182:5, AR189:5, AR201:5, AR166:5, AR261:5, AR089:5, AR313:5, AR193:5, AR177:4, AR246:4, AR255:4, AR216:4, AR285:4, AR179:4, AR257:4, AR217:4, AR170:4, AR221:4, AR290:4, AR299:4, AR252:4, AR200:4, AR267:4, AR262:4, AR235:4, AR185:4, AR240:4, AR238:4, AR233:4, AR295:4, AR316:4, AR168:4, AR190:4, AR218:4, AR271:4, AR236:4, AR296:4, AR096:4, AR287:4, AR199:4, AR293:4, AR272:4, AR242:4, AR297:4, AR243:4, AR294:4, AR195:4, AR300:4, AR169:3, AR224:3, AR253:3, AR282:3, AR203:3, AR239:3, AR033:3, AR288:3, AR309:3, AR171:3, AR222:3, AR211:3, AR312:3, AR275:3, AR231:3, AR232:3, AR192:3, AR247:3, AR260:3, AR228:3, AR104:3, AR283:3, AR229:3, AR210:3, AR225:3, AR039:3, AR258:3, AR205:3, AR234:3, AR286:3, AR289:3, AR308:3, AR230:3, AR263:3, AR219:3, AR237:3, AR214:3, AR277:2, AR204:2, AR227:2, AR274:2, AR256:2, AR226:2, AR061:2, AR245:2, AR212:2, AR213:2, AR311:1 H0351:10, L0439:4, L0766:3, L3255:2, L2562:2, L0775:2, L0666:2, L0779:2, L0780:2, L0755:2, L0731:2, H0772:1, L3388:1, H0333:1, H0486:1, H0015:1, H0687:1, S0422:1, L0761:1, L0776:1, L0659:1, L0663:1, H0682:1, S0152:1, L0745:1, L0752:1 and S0026:1.
94	HHBCS39	1003028	104	AR218:14, AR219:12, AR096:11, AR309:8, AR192:7, AR195:7, AR165:6, AR263:6, AR164:6, AR224:6, AR245:6,



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	HHBCS39	847543	305	
95	HHEAA08	638231	105	AR192:9, AR246:7, AR217:7, AR224:7, AR214:7, AR197:7, AR207:6, AR250:6, AR195:6, AR216:6, AR169:6, AR039:6, AR089:6, AR271:6, AR223:5, AR312:5, AR212:5, AR313:5, AR222:5, AR282:5, AR165:5, AR196:5, AR053:5, AR162:5, AR161:5, AR164:5, AR166:5, AR254:5, AR263:5, AR193:5, AR225:5, AR309:5, AR163:5, AR311:5, AR205:5, AR299:5, AR235:4, AR243:4, AR295:4, AR264:4, AR274:4, AR245:4, AR300:4, AR213:4, AR172:4, AR275:4, AR201:4, AR191:4, AR060:4, AR308:4, AR175:4, AR261:4, AR240:4, AR221:4, AR296:4, AR174:4, AR316:4, AR178:4, AR171:4, AR272:4, AR242:4, AR199:4, AR177:3, AR096:3, AR288:3, AR168:3, AR033:3, AR104:3, AR291:3, AR257:3, AR200:3, AR188:3, AR218:3, AR173:3, AR183:3, AR285:3, AR198:3, AR180:3, AR189:3, AR283:3, AR270:3, AR268:3, AR262:3, AR247:3, AR293:3, AR286:3, AR297:3, AR238:3, AR236:3, AR185:3, AR237:3, AR190:3, AR181:3, AR258:2, AR226:2, AR182:2, AR232:2, AR287:2, AR277:2, AR289:2, AR203:2, AR266:2, AR294:2, AR267:2, AR290:2, AR204:2, AR239:2, AR255:2, AR231:2, AR229:2, AR233:2, AR256:2, AR269:2, AR210:2, AR219:2, AR234:2, AR179:2, AR227:2, AR211:1, AR055:1, AR260:1, AR230:1, AR253:1, AR061:1, AR228:1, AR215:1, H0341:1 and H0542:1.
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96	HHENV10	562772	106	AR242:3, AR235:3, AR183:3, AR309:3, AR282:3, AR243:2, AR171:2, AR283:1, AR055:1, AR257:1, AR168:1, AR213:1, AR164:1, AR230:1, AR264:1, AR287:1, H0543:2, H0497:1 and H0625:1.
97	HHFFJ48	634521	107	AR221:4, AR235:3, AR180:3, AR192:3, AR277:3, AR252:3, AR245:2, AR215:2, AR183:2, AR308:2, AR214:2, AR195:2, AR282:2, AR205:2, AR270:2, AR171:2, AR223:2, AR175:1, AR230:1, AR264:1, AR176:1, AR162:1, AR213:1, AR261:1, AR161:1, AR297:1, AR226:1, H0580:1 and H0050:1.
98	HHFHJ59	411332	108	AR241:5, AR249:5, AR310:5, AR186:4, AR251:4, AR052:4, AR282:3, AR171:3, AR055:3, AR309:3, AR224:3, AR176:3, AR033:3, AR248:3, AR184:3, AR206:3, AR247:3, AR061:2, AR312:2, AR180:2, AR253:2, AR183:2, AR204:2, AR265:2, AR217:2, AR295:2, AR299:2, AR188:2, AR264:2, AR268:2, AR292:2, AR198:2, AR238:2,

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101	HHGCM76	662329	111	AR245:8, AR175:7, AR183:6, AR176:6, AR196:6, AR191:6, AR174:6, AR060:5, AR254:5, AR263:5, AR039:5, AR173:5, AR177:5, AR309:5, AR261:5, AR232:4, AR161:4, AR162:4, AR096:4, AR163:4, AR182:4, AR264:4, AR089:4, AR165:4, AR198:4, AR270:4, AR275:4, AR268:4, AR178:4, AR189:4, AR164:4, AR166:3, AR286:3, AR242:3, AR193:3, AR243:3, AR216:3, AR171:3, AR283:3, AR266:3, AR215:3, AR272:3, AR211:3, AR188:3, AR313:3, AR180:3, AR207:3, AR269:3, AR200:3, AR247:3, AR316:3, AR289:3, AR290:3, AR229:3, AR294:3, AR297:3, AR195:3, AR267:3, AR061:3, AR240:3, AR295:3, AR197:3, AR238:3, AR257:3, AR190:3, AR055:3, AR228:2, AR181:2, AR053:2, AR033:2, AR288:2, AR226:2, AR201:2, AR239:2, AR287:2, AR231:2,

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102	HHGCQ54	544615	112	AR215:4, AR180:3, AR161:3, AR162:3, AR170:3, AR163:3, AR245:2, AR291:2, AR236:2, AR168:2, AR270:2, AR282:2, AR053:2, AR285:2, AR096:2, AR089:2, AR262:2, AR222:2, AR189:2, AR060:2, AR226:2, AR266:1, AR289:1, AR181:1, AR164:1, AR225:1, AR242:1, AR183:1, AR178:1, AR257:1, AR287:1, AR295:1, AR261:1, AR172:1, AR165:1, AR203:1, AR204:1, AR297:1, AR166:1, AR240:1, AR239:1, AR237:1, AR294:1, AR190:1, AR311:1, AR033:1, AR216:1, AR255:1, AR267:1, AR224:1, L0439:9, S0434:8, L0637:3, L0780:3, L0662:2, L0790:2, L0438:2, S0404:2, L0751:2, L0777:2, H0149:1, S0358:1, S0444:1, H0778:1, H0333:1, S0049:1, H0024:1, H0135:1, H0413:1, H0100:1, H0647:1, L0772:1, L0659:1, L0809:1 and L0759:1.
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105	HJACG02	1307789	115	<p>AR207:37, AR195:33, AR283:32, AR263:32, AR264:29, AR223:28, AR214:28, AR089:28, AR277:27, AR222:27, AR309:27, AR311:27, AR212:26, AR169:26, AR316:25, AR224:24, AR096:24, AR055:24, AR197:23, AR213:23, AR282:22, AR104:22, AR245:22, AR171:22, AR218:22, AR162:22, AR192:21, AR217:21, AR161:21, AR193:21, AR163:20, AR308:20, AR165:20, AR168:20, AR216:20, AR170:20, AR164:20, AR235:19, AR172:19, AR053:19, AR166:19, AR060:19, AR219:19, AR242:19, AR271:19, AR299:19, AR210:19, AR039:19, AR033:19, AR240:18, AR225:18, AR313:18, AR312:18, AR201:18, AR221:17, AR261:17, AR198:17, AR246:17, AR288:17, AR252:17, AR295:17, AR176:16, AR177:16, AR215:15, AR297:15, AR253:15, AR205:15, AR270:15, AR196:15, AR185:15, AR275:15, AR286:15, AR285:14, AR260:14, AR287:14, AR233:14, AR236:14, AR183:14, AR227:13, AR175:13, AR211:13, AR300:13, AR250:13, AR294:13, AR181:13, AR274:13, AR272:13, AR229:13, AR174:12, AR256:12, AR182:12, AR234:12, AR204:12, AR269:12, AR228:12, AR293:12, AR178:12, AR226:12, AR268:11, AR266:11, AR173:11, AR262:11, AR200:11, AR243:11, AR199:11, AR258:11, AR231:11, AR291:11, AR180:11, AR289:11, AR247:11, AR239:10, AR257:10, AR267:10, AR255:10, AR188:10, AR254:10, AR203:10, AR232:10, AR238:9, AR191:9, AR189:9, AR190:9, AR061:9, AR230:9, AR296:9, AR179:9, AR290:8, AR237:7 S0442:4, L0764:4, S0408:3, H0306:2, H0263:2, H0596:2, L0800:2, L0755:2, S0116:1, S0358:1, H0489:1, H0597:1, T0041:1 and L0772:1.</p>
	HJACG02	509948	308	
106	HJACG30	895505	116	<p>AR263:8, AR165:8, AR250:8, AR162:7, AR161:7, AR205:7, AR196:7, AR166:7, AR164:7, AR215:7, AR163:7, AR192:7, AR198:7, AR235:7, AR245:6, AR264:6, AR216:6, AR270:6, AR207:6, AR309:6, AR246:6, AR174:5, AR223:5, AR269:5, AR168:5, AR243:5, AR224:5, AR180:5, AR311:5, AR183:5, AR308:5, AR254:5, AR173:5, AR177:5, AR268:5, AR242:5, AR179:5, AR312:5, AR176:5, AR175:5, AR291:5, AR221:5, AR181:5, AR285:4, AR170:4, AR275:4, AR295:4, AR053:4, AR271:4, AR191:4, AR288:4, AR204:4, AR316:4, AR274:4, AR199:4,</p>

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107	HJBCY35	719729	117	AR215:11, AR291:11, AR225:10, AR217:9, AR216:8, AR296:8, AR214:8, AR297:8, AR266:7, AR183:7, AR257:7, AR223:7, AR170:7, AR269:7, AR287:7, AR221:6, AR270:6, AR171:6, AR182:6, AR286:6, AR169:6, AR172:6, AR294:6, AR176:6, AR235:6, AR163:5, AR295:5, AR161:5, AR168:5, AR255:5, AR162:5, AR224:5, AR285:5, AR293:5, AR268:5, AR289:5, AR288:5, AR263:5, AR264:5, AR165:4, AR173:4, AR260:4, AR262:4, AR175:4, AR164:4, AR179:4, AR055:4, AR104:4, AR222:4, AR166:4, AR060:4, AR181:4, AR242:4, AR243:4, AR283:4, AR258:4, AR240:4, AR311:4, AR290:3, AR180:3, AR282:3, AR247:3, AR231:3, AR316:3, AR267:3, AR233:3, AR228:3, AR300:3, AR236:3, AR177:3, AR096:3, AR212:3, AR256:3, AR275:3, AR237:3, AR185:3, AR239:3, AR299:3, AR245:3, AR229:3, AR039:3, AR238:3, AR234:3, AR191:3, AR190:2, AR199:2, AR089:2, AR178:2, AR277:2, AR189:2, AR174:2, AR205:2, AR309:2, AR061:2, AR274:2, AR227:2, AR261:2, AR188:2, AR218:2, AR272:2, AR219:2, AR312:2, AR196:2, AR195:2, AR232:2, AR200:2, AR211:2, AR230:2, AR203:1, AR210:1, AR226:1, AR033:1, AR252:1 H0618:16, H0617:13, H0253:11, H0457:6, L0766:6, L0769:5, H0255:4, H0559:4, H0181:4, L0748:4, H0170:3, S0051:3, H0622:3, L0770:3, L0653:3, L0743:3, L0779:3, H0341:2, H0484:2, S0049:2, H0620:2, H0424:2, H0135:2, H0040:2, H0059:2, H0100:2, T0042:2, S0002:2, L0758:2, L0588:2, H0171:1, S0134:1, H0650:1, H0657:1, H0656:1, S0116:1, L0534:1, H0637:1, S6026:1, S0300:1, L0717:1, H0549:1, H0550:1, S6014:1, H0333:1, L2504:1, L2522:1, H0427:1, L0021:1, H0599:1, H0545:1, H0150:1, L0157:1, S0050:1, H0355:1, H0252:1, L0483:1, H0068:1, S0036:1, H0038:1, H0087:1, H0272:1, H0623:1, T0041:1, L4747:1, L3904:1, L3905:1, L0761:1, L0645:1, L0648:1, L0662:1, L0768:1, L0774:1, L0776:1, L0658:1, L4669:1, L0659:1, L0382:1, L0665:1, L2257:1, L2260:1, H0547:1, H0711:1, H0670:1, H0672:1, S0350:1, H0696:1, H0704:1, L0744:1, L0439:1, L0749:1, L0777:1, L0780:1, L0731:1, L0757:1, S0436:1, S0276:1 and H0543:1.
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114	HKFBC53	1352286	124		AR249:155, AR248:131, AR251:111, AR265:54, AR253:42, AR096:23, AR263:23, AR244:18, AR290:13, AR268:13, AR246:12, AR184:11, AR177:11, AR194:9, AR267:8, AR229:8, AR270:8, AR247:7, AR240:7, AR269:7, AR183:6, AR202:5, AR175:5, AR234:5, AR241:5, AR316:5, AR206:5, AR313:5, AR055:4, AR299:4, AR033:4, AR238:3, AR292:3, AR061:3, AR182:3, AR171:3, AR273:3, AR224:3, AR274:3, AR198:3, AR275:3, AR216:3, AR266:3, AR195:3, AR284:3, AR168:3, AR237:2, AR215:2, AR282:2, AR285:2, AR242:2, AR310:2, AR250:2, AR300:2, AR298:2, AR186:2, AR039:2, AR231:2, AR291:2, AR223:2, AR243:2, AR289:2, AR179:2, AR204:2, AR104:2, AR205:2, AR257:2, AR271:2, AR053:2, AR226:2, AR277:2, AR217:2, AR232:2, AR192:2, AR296:2, AR185:2, AR264:1, AR295:1, AR089:1, AR261:1, AR213:1, AR259:1, AR166:1, AR286:1, AR308:1, AR233:1, AR201:1, L0794:11, H0521:11, S0002:8, L0805:8, L0803:7, S0278:6, S0144:6, L0774:4, L0777:4, S0380:3, H0265:2, H0556:2, H0255:2, H0638:2, L0761:2, L0776:2, L0809:2, S0406:2, S0298:1, S0420:1, S0356:1, H0431:1, H0618:1, H0546:1, H0100:1, H0429:1, H0494:1, H0509:1, S0142:1, S0426:1, L0640:1, L0763:1, L0770:1, L3904:1, L0800:1, L0804:1, L0806:1, L0807:1, L4669:1, L5622:1, L5623:1, L0791:1, L0792:1, L0666:1, L2261:1, S0374:1, H0690:1, H0522:1, S0390:1, L0740:1, L0751:1, L0756:1, L0779:1 and L0731:1.
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	HKFBC53	513190	318		
	HKFBC53	383426	319		
115	HKGDL36	877489	125		AR274:28, AR214:24, AR168:23, AR216:22, AR205:21, AR245:20, AR224:20, AR272:18, AR222:17, AR199:17, AR171:17, AR223:17, AR252:17, AR215:16, AR213:16, AR312:16, AR195:15, AR217:15, AR170:15, AR247:15, AR166:14, AR313:14, AR212:14, AR246:14, AR225:14, AR165:13, AR164:13, AR172:13, AR311:13, AR308:13, AR169:12, AR162:12, AR161:12, AR053:12, AR221:12, AR163:12, AR210:11, AR179:11, AR188:11, AR197:10, AR275:10, AR263:10, AR250:10, AR189:9, AR174:9, AR264:9, AR242:9, AR236:9, AR089:9, AR201:9, AR254:9, AR096:9, AR193:8, AR299:8, AR271:8, AR243:8, AR175:8, AR309:8, AR253:8, AR039:8, AR291:8, AR180:8, AR296:8, AR190:7, AR185:7, AR288:7, AR173:7, AR240:7, AR178:7, AR295:7, AR293:7, AR218:7, AR267:7, AR183:6, AR211:6, AR289:6, AR282:6, AR262:6, AR191:6, AR300:6, AR219:6, AR277:6, AR316:6, AR192:6, AR290:6, AR270:6, AR177:6, AR261:6, AR269:6, AR268:6, AR266:6, AR255:6, AR060:6, AR204:6, AR297:6, AR231:5, AR203:5, AR200:5, AR230:5, AR257:5, AR285:5, AR198:5, AR237:5, AR294:5, AR256:5, AR283:5, AR181:5, AR287:4, AR239:4, AR260:4, AR229:4, AR258:4, AR104:4, AR234:4, AR233:4, AR061:4, AR207:4, AR182:4, AR176:4, AR286:4, AR232:4, AR238:3, AR033:3, AR226:3, AR196:3, AR055:3, AR227:3, AR235:2, AR228:2, H0424:28, L0803:25, L0805:9, L0636:7, L0774:5, L0770:4, H0661:2, S0222:2, L0157:2, L0638:2, L3904:2, L0776:2, L0659:2, L0809:2, L0789:2, H0539:2, L0592:2, H0295:1, S0114:1, H0663:1, S6026:1, H0549:1, H0748:1, H0571:1, S0051:1, T0006:1, H0033:1, H0604:1, H0213:1, H0418:1, H0417:1, H0538:1, L0769:1, L3905:1, L0794:1, L0647:1, L0787:1, H0684:1, H0672:1, L0749:1, L0753:1, L0759:1, S0260:1, S0434:1 and S0436:1.



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116	HKISB57	625956	126	<p>AR161:12, AR162:12, AR163:12, AR165:12, AR164:11, AR166:11, AR089:8, AR225:7, AR178:6, AR183:6, AR172:6, AR300:5, AR224:5, AR181:5, AR221:5, AR223:5, AR170:5, AR299:5, AR039:4, AR291:4, AR096:4, AR268:4, AR275:4, AR286:4, AR274:4, AR055:4, AR222:4, AR269:4, AR258:4, AR257:4, AR179:3, AR240:3, AR242:3, AR173:3, AR182:3, AR262:3, AR270:3, AR272:3, AR189:3, AR316:3, AR267:3, AR175:3, AR245:3, AR313:3, AR287:3, AR296:3, AR231:2, AR210:2, AR171:2, AR190:2, AR217:2, AR205:2, AR277:2, AR230:2, AR295:2, AR290:2, AR263:2, AR060:2, AR309:2, AR191:2, AR228:2, AR229:2, AR104:2, AR261:2, AR288:2, AR174:2, AR282:2, AR246:2, AR255:2, AR312:2, AR237:2, AR169:2, AR193:2, AR271:2, AR201:2, AR233:2, AR239:2, AR197:1, AR061:1, AR226:1, AR177:1, AR213:1, AR195:1, AR033:1, AR188:1, AR238:1, AR196:1, AR185:1, AR293:1, AR176:1, AR234:1, AR227:1, L0747:5, L0731:5, H0031:4, L0599:4, S0045:3, H0411:3, H0494:3, L0783:3, L0743:3, L0758:3, L0759:3, L0604:3, H0295:2, S0356:2, S0360:2, S0046:2, H0413:2, L0774:2, H0651:2, S0027:2, L0748:2, L0439:2, L0752:2, L0601:2, H0484:1, S0132:1, H0586:1, H0333:1, H0486:1, H0042:1, H0122:1, H0546:1, H0041:1, H0050:1, H0408:1, H0288:1, H0688:1, H0424:1, H0644:1, H0383:1, L0772:1, L0764:1, L0662:1, L0364:1, L0653:1, L0782:1, L0789:1, L0666:1, L0663:1, L0664:1, H0144:1, S0148:1, H0593:1, H0666:1, S0330:1, S0044:1, S0037:1, S3014:1, L0757:1, S0031:1, H0667:1 and H0506:1.</p>
117	HKMMW74	581399	127	<p>AR229:11, AR313:11, AR163:10, AR162:10, AR161:10, AR242:9, AR176:9, AR039:9, AR204:9, AR197:8, AR309:8, AR192:8, AR180:8, AR264:8, AR181:8, AR178:8, AR089:8, AR177:8, AR164:8, AR247:7, AR268:7, AR196:7, AR239:7, AR166:7, AR182:7, AR252:7, AR271:7, AR246:7, AR282:7, AR300:7, AR165:7, AR269:7, AR233:7, AR173:7, AR174:7, AR179:7, AR267:6, AR236:6, AR228:6, AR238:6, AR175:6, AR198:6, AR096:6, AR060:6, AR299:6, AR235:6, AR257:6, AR240:6, AR261:6, AR055:6, AR293:6, AR275:6, AR226:5, AR237:5, AR185:5, AR183:5, AR243:5, AR201:5, AR234:5, AR195:5, AR250:5, AR207:5, AR291:5, AR245:5, AR316:5, AR266:5, AR191:5, AR312:5, AR053:5, AR227:5, AR231:5, AR254:5, AR230:5, AR262:5, AR270:5, AR203:5, AR224:4, AR289:4, AR263:4, AR285:4, AR212:4, AR193:4, AR199:4, AR258:4, AR216:4, AR218:4, AR061:4, AR213:4, AR255:4, AR217:4, AR297:4, AR277:4, AR200:4, AR104:4, AR272:4, AR232:4, AR205:4, AR274:4, AR296:4, AR295:3, AR286:3, AR033:3, AR189:3, AR287:3, AR290:3, AR256:3, AR190:3, AR311:3, AR283:3, AR169:3, AR168:3, AR170:3, AR215:3, AR253:3, AR308:3, AR288:3, AR188:3, AR171:3, AR214:3, AR223:3, AR219:2, AR294:2, AR221:2, AR260:2, AR222:2, AR172:2, AR210:1, AR225:1, H0431:1</p>
118	HLDNA86	1352197	128	<p>AR314:215, AR280:182, AR186:162, AR298:160, AR315:158, AR241:158, AR259:155, AR227:154, AR055:144, AR233:143, AR281:140, AR275:136, AR232:134, AR192:131, AR061:131, AR175:130, AR284:127, AR194:125, AR204:120, AR295:120, AR237:117, AR285:116, AR033:112, AR286:111, AR184:108, AR185:107, AR226:107, AR238:107, AR293:105, AR177:100, AR198:100, AR231:100, AR299:100, AR300:99, AR206:99, AR202:97, AR271:95, AR052:94, AR273:91, AR104:84, AR243:84, AR179:83, AR292:80, AR294:77, AR283:71, AR291:71, AR229:68, AR244:67, AR282:66, AR267:63, AR234:63, AR053:61, AR182:60, AR039:59, AR310:57, AR205:57, AR183:56, AR274:56, AR060:51, AR089:49, AR247:49, AR296:48, AR251:46, AR240:46, AR269:46, AR309:45, AR316:45, AR213:43, AR258:42, AR096:40, AR246:39, AR289:38, AR265:38, AR290:37, AR268:36, AR270:36, AR211:35, AR256:34, AR312:33, AR277:32, AR161:32, AR162:32, AR218:32, AR228:31, AR163:29, AR239:29,</p>

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125	HLQDR48	1307726	135	AR237:8, AR238:7, AR232:7, AR229:6, AR207:6, AR228:5, AR282:4, AR234:4, AR227:3, AR230:3, AR233:3,

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126	HLTHR66	699812	136	AR282:6, AR221:4, AR235:3, AR176:3, AR266:3, AR215:3, AR269:3, AR171:3, AR270:3, AR308:2, AR183:2, AR196:2, AR217:2, AR172:2, AR177:2, AR197:2, AR222:2, AR268:2, AR295:2, AR228:2, AR236:2, AR267:2, AR188:2, AR238:2, AR261:2, AR309:2, AR255:2, AR296:2, AR233:2, AR207:2, AR291:2, AR257:2, AR290:2, AR232:2, AR193:1, AR277:1, AR178:1, AR283:1, AR089:1, AR181:1, AR164:1, AR203:1, AR264:1, AR212:1, AR166:1, AR231:1, AR247:1, AR293:1, AR205:1, AR055:1, AR316:1, AR300:1, AR175:1, AR287:1, AR189:1, AR168:1, AR234:1, AR161:1, AR174:1, AR239:1 H0036:2, S0132:1, S0010:1, S0250:1, H0591:1 and H0130:1.
127	HLTIP94	1087335	137	AR060:7, AR055:7, AR185:6, AR313:6, AR218:5, AR300:5, AR240:5, AR089:4, AR282:4, AR299:4, AR283:4, AR039:3, AR096:3, AR316:3, AR104:3, AR277:3, AR219:2 H0170:1, S6026:1 and H0591:1.
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216	HSYAZ63	1177537	226	<p>AR179:11, AR218:11, AR293:11, AR164:11, AR233:11, AR182:11, AR257:11, AR316:11, AR166:11, AR196:10, AR178:10, AR264:10, AR277:10, AR180:10, AR236:10, AR174:10, AR181:10, AR191:9, AR275:9, AR270:9, AR234:9, AR060:9, AR176:9, AR255:8, AR200:8, AR177:8, AR242:8, AR199:8, AR260:8, AR238:8, AR285:8, AR294:8, AR104:8, AR296:8, AR266:8, AR312:8, AR189:7, AR226:7, AR053:7, AR261:7, AR192:7, AR287:7, AR297:7, AR231:7, AR291:7, AR197:7, AR219:7, AR237:7, AR033:7, AR055:7, AR268:6, AR203:6, AR290:6, AR282:6, AR228:6, AR286:6, AR274:6, AR267:6, AR215:6, AR288:6, AR239:6, AR188:6, AR230:6, AR207:5, AR309:5, AR168:5, AR295:5, AR204:5, AR212:5, AR213:5, AR198:5, AR235:5, AR263:5, AR271:4, AR201:4, AR190:4, AR308:4, AR272:4, AR211:4, AR227:4, AR283:4, AR243:4, AR172:4, AR205:4, AR256:4, AR245:4, AR221:4, AR289:4, AR225:3, AR210:3, AR195:3, AR061:3, AR214:3, AR246:3, AR232:3, AR223:3, AR311:3, AR171:3, AR224:2, AR169:2, AR193:2, AR222:2, AR217:2, AR170:1, L0439:15, L0752:6, L0758:6, L0438:5, L0731:5, L0803:4, H0171:3, L0717:3, H0251:3, L0142:3, S0036:3, S0422:3, L0764:3, L0659:3, L0666:3, L0664:3, S0380:3, L0754:3, L0759:3, L0591:3, L0608:3, H0624:2, T0002:2, H0486:2, H0052:2, L0471:2, H0375:2, S0002:2, L0771:2, L0766:2, L0776:2, L0517:2, L0665:2, S0330:2, S0028:2, L0747:2, L0749:2, L0750:2, H0445:2, L0603:2, H0170:1, H0685:1, L0785:1, H0341:1, S0298:1, S0212:1, S0282:1, H0255:1, S0418:1, T0007:1, S0358:1, S0360:1, H0580:1, S0007:1, S0045:1, S0046:1, H0393:1, H0351:1, H0441:1, L0586:1, H0042:1, H0575:1, H0318:1, H0581:1, H0309:1, H0457:1, H0050:1, H0083:1, H0354:1, S0003:1, S0214:1, L0483:1, H0553:1, L0143:1, H0163:1, H0591:1, H0551:1, H0413:1, L0564:1, H0022:1, H0494:1, H0649:1, L0598:1, L0369:1, L0640:1, L0763:1, L0770:1, L0638:1, L0761:1, L0667:1, L0772:1, L0646:1, L0521:1, L0774:1, L0375:1, L0806:1, L0655:1, L0606:1, L0656:1, L0783:1, L0809:1, L0530:1, L0790:1, S0428:1, H0144:1, S0148:1, H0659:1, H0670:1, H0539:1, L0602:1, S0406:1, L0744:1, L0740:1, L0745:1, L0777:1, L0753:1, H0444:1, L0596:1, L0589:1, L0605:1, L0599:1, L0362:1, S0026:1, H0653:1, S0196:1, S0456:1 and L0600:1.</p>
216	HSYAZ63	1177537	226	<p>AR216:22, AR214:19, AR096:18, AR172:17, AR215:15, AR217:14, AR222:14, AR224:13, AR291:13, AR274:13, AR168:13, AR171:12, AR223:12, AR219:12, AR285:12, AR287:12, AR297:12, AR170:12, AR271:11, AR225:11, AR247:11, AR169:11, AR218:11, AR221:10, AR165:10, AR212:10, AR164:10, AR283:10, AR275:10, AR166:9, AR311:9, AR161:9, AR289:9, AR162:9, AR213:9, AR235:9, AR309:9, AR163:9, AR205:9, AR312:9, AR261:9, AR308:9, AR295:8, AR296:8, AR226:8, AR238:8, AR293:8, AR250:8, AR313:7, AR246:7, AR272:7, AR193:7, AR263:7, AR240:7, AR262:7, AR198:7, AR053:7, AR255:7, AR316:7, AR264:7, AR258:7, AR245:6, AR231:6, AR288:6, AR237:6, AR178:6, AR286:6, AR236:6, AR257:6, AR242:6, AR294:6, AR197:6, AR256:6, AR269:6, AR270:6, AR173:5, AR290:5, AR195:5, AR192:5, AR181:5, AR207:5, AR243:5, AR239:5, AR227:5, AR266:5, AR177:5, AR174:5, AR268:5, AR188:5, AR179:5, AR211:5, AR176:5, AR282:4, AR230:4, AR299:4, AR196:4, AR185:4, AR190:4, AR183:4, AR277:4, AR199:4, AR180:4, AR175:4, AR234:4, AR189:4, AR260:4, AR254:4, AR039:4, AR229:4, AR232:4, AR233:4, AR191:4, AR089:4, AR061:4, AR267:3, AR201:3, AR055:3, AR253:3, AR210:3, AR200:3, AR300:3, AR203:3, AR060:3, AR204:2, AR182:2, AR033:2, AR228:2, AR104:1, H0521:40, H0046:18, H0522:11, L0747:8, L0750:8, S0002:7, L0439:7, L0754:7, H0486:6, L0595:6, H0556:5, H0551:5, H0024:4, H0622:4, S0344:4, H0519:4, L0740:4, L0751:4, L0759:4, L0599:4, H0580:3, H0013:3, H0581:3, S0051:3, L0369:3, H0402:2, S0356:2, S0360:2, S0045:2, S0046:2, H0411:2, H0574:2, L0021:2, H0575:2, H0594:2, H0266:2, S0214:2,</p>

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	HSYAZ63	862063	375	
217	HSYBG37	1056317	227	<p>AR216:52, AR214:45, AR205:44, AR215:39, AR199:38, AR274:34, AR222:33, AR217:33, AR225:33, AR172:31, AR171:30, AR168:30, AR223:29, AR245:28, AR169:28, AR224:27, AR170:27, AR210:25, AR221:24, AR272:24, AR175:23, AR247:22, AR246:22, AR195:21, AR213:21, AR218:20, AR212:20, AR189:19, AR211:19, AR053:19, AR188:18, AR089:18, AR096:18, AR173:18, AR185:18, AR191:17, AR312:17, AR164:16, AR299:16, AR104:16, AR174:16, AR219:16, AR192:16, AR177:16, AR313:16, AR161:16, AR163:16, AR162:16, AR275:16, AR039:15, AR166:15, AR165:15, AR197:15, AR236:15, AR291:15, AR190:15, AR254:14, AR290:14, AR261:14, AR316:14, AR240:14, AR282:14, AR183:14, AR182:14, AR179:14, AR311:13, AR181:13, AR060:13, AR271:13, AR256:13, AR295:13, AR288:13, AR250:13, AR266:12, AR243:12, AR242:12, AR268:12, AR262:12, AR309:12, AR308:12, AR178:12, AR267:12, AR270:12, AR200:12, AR300:12, AR196:12, AR269:12, AR203:12, AR296:11, AR198:11, AR180:11, AR283:11, AR255:10, AR257:10, AR277:10, AR230:10, AR252:10, AR239:9, AR289:9, AR231:9, AR263:9, AR297:9, AR285:9, AR201:9, AR237:9, AR238:9, AR293:9, AR204:9, AR033:9, AR264:9, AR253:8, AR260:8, AR061:8, AR193:8, AR229:8, AR287:8, AR258:8, AR232:7, AR176:7, AR234:7, AR233:7, AR294:6, AR226:6, AR286:6, AR227:6, AR235:6, AR055:5, AR228:4, AR207:4 L0770:3, S0442:2, S0358:2, L0769:2, S0380:2, H0717:1, S6024:1, H0656:1, H0341:1, H0409:1, H0486:1, L2637:1, T0060:1, H0156:1, H0036:1, H0421:1, H0052:1, H0544:1, H0551:1, H0059:1, S0142:1, L3904:1, L3905:1, L0378:1, L5622:1, L0709:1, L2263:1, L3811:1, H0547:1, L0602:1, L0611:1, L0742:1, L0748:1, L0439:1, L0756:1, L0777:1, L0731:1, S0434:1 and L0599:1.</p>
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218	HTADW91	844835	228	<p>AR218:11, AR219:10, AR281:10, AR280:8, AR060:7, AR055:7, AR177:7, AR183:7, AR315:7, AR089:6, AR292:6, AR314:5, AR316:5, AR247:5, AR104:5, AR293:5, AR295:5, AR175:5, AR283:4, AR299:4, AR033:4, AR251:4, AR294:4, AR096:4, AR249:4, AR282:4, AR253:4, AR259:4, AR258:3, AR240:3, AR269:3, AR185:3, AR277:3, AR313:3, AR184:3, AR256:3, AR182:3, AR290:3, AR286:3, AR284:3, AR266:3, AR233:3, AR267:3, AR192:3, AR039:2, AR296:2, AR238:2, AR310:2, AR298:2, AR300:2, AR061:2, AR270:2, AR179:2, AR291:2, AR227:2, AR231:2, AR285:2, AR268:2, AR226:2, AR234:1, AR274:1, AR263:1, AR312:1 H0618:12, L0743:10, L0794:9, L0803:9, L0758:9, L0731:8, L0748:7, L0754:6, H0545:5, H0658:5, H0052:4, H0546:4, L0648:4, L0662:4, L0774:4, L0665:4, L0779:4, H0135:3, L0659:3, H0547:3, H0521:3, L0751:3, L0747:3, H0295:2, H0657:2, H0306:2, S0420:2,</p>

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219	HTAEE28	1018291	229	AR170:5, AR169:4, AR221:3, AR250:3, AR217:3, AR242:2, AR263:2, AR171:2, AR193:2, AR245:2, AR201:2, AR172:2, AR183:2, AR300:2, AR216:1, AR267:1, AR309:1, AR257:1, AR269:1, AR224:1, AR168:1, AR161:1, AR215:1, AR311:1, H0250:3, H0069:2, L0771:2, S0404:2, H0650:1, H0656:1, H0486:1, H0013:1, H0318:1, S0422:1, L0644:1, L0768:1, L0794:1, L0804:1, L0655:1, L0789:1, L0664:1, H0436:1 and L0758:1.
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	HTAEE28	864120	378	
220	HTDAF28	396835	230	AR214:19, AR263:19, AR223:19, AR224:17, AR222:17, AR207:16, AR311:16, AR170:15, AR168:15, AR169:15, AR264:14, AR165:14, AR217:14, AR215:14, AR164:14, AR166:13, AR235:13, AR216:13, AR225:13, AR308:13, AR171:13, AR221:12, AR261:12, AR245:12, AR161:12, AR195:11, AR162:11, AR163:11, AR172:11, AR242:10, AR295:10, AR192:10, AR196:10, AR288:10, AR297:10, AR089:10, AR312:10, AR198:9, AR291:9, AR240:9, AR210:9, AR277:9, AR060:9, AR309:9, AR205:9, AR282:9, AR246:9, AR177:9, AR200:9, AR197:9, AR289:8, AR316:8, AR253:8, AR286:8, AR300:8, AR181:8, AR104:8, AR247:8, AR296:8, AR039:8, AR096:8, AR285:8, AR293:7, AR313:7, AR287:7, AR201:7, AR283:7, AR212:7, AR180:7, AR053:7, AR236:7, AR174:7, AR183:7, AR299:7, AR269:7, AR176:7, AR266:7, AR199:7, AR203:7, AR272:6, AR270:6, AR290:6, AR193:6, AR239:6, AR237:6, AR231:6, AR230:6, AR191:6, AR258:6, AR189:6, AR268:6, AR262:6, AR188:6, AR204:6, AR234:6, AR175:6, AR257:6, AR061:5, AR213:5, AR173:5, AR218:5, AR238:5, AR179:5, AR294:5, AR255:5, AR178:5, AR182:5, AR267:5, AR256:5, AR219:5, AR260:5, AR254:5, AR211:5, AR274:5, AR252:5, AR232:5, AR271:5, AR275:5, AR033:5, AR190:5, AR055:4, AR229:4, AR227:4, AR228:4, AR233:4, AR243:4, AR226:4, AR185:3, AR250:2, H0551:4, L0665:3, S0356:2, S0360:2, L0662:2, L0527:2, L0666:2, L0754:2, H0333:1, H0012:1, H0688:1, H0553:1, H0477:1, L0770:1, L0769:1, L0650:1, L0606:1, L0790:1, H0520:1, H0547:1, H0682:1, L0747:1, L0779:1 and L0755:1.
221	HTECC05	1352365	231	AR176:5, AR169:3, AR224:3, AR180:3, AR291:3, AR225:3, AR238:3, AR267:3, AR261:2, AR245:2, AR289:2, AR270:2, AR257:2, AR175:2, AR269:2, AR168:2, AR181:2, AR228:2, AR243:2, AR309:2, AR285:2, AR295:2, AR217:2, AR230:2, AR293:2, AR239:2, AR171:2, AR177:2, AR294:2, AR236:2, AR313:1, AR296:1, AR231:1, AR290:1, AR190:1, AR227:1, AR179:1, AR246:1, AR312:1, AR287:1, AR247:1, AR266:1, AR178:1, AR250:1, AR061:1, AR182:1, AR268:1, AR233:1, AR196:1, AR262:1, AR234:1, AR272:1, AR162:1, AR277:1,

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	HTECC05	666743	380	
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236	HTXAJ12	1310814	246	AR176:10, AR162:10, AR161:10, AR201:10, AR163:10, AR271:10, AR204:9, AR192:9, AR229:9, AR266:9, AR309:9, AR254:9, AR197:8, AR180:8, AR215:8, AR178:8, AR228:8, AR183:7, AR207:7, AR269:7, AR216:7, AR253:7, AR165:7, AR237:7, AR267:7, AR182:7, AR164:7, AR239:6, AR272:6, AR166:6, AR055:6, AR268:6, AR233:6, AR170:6, AR061:6, AR250:6, AR181:6, AR193:6, AR238:6, AR198:6, AR291:6, AR270:6, AR261:6, AR289:6, AR053:6, AR243:6, AR226:6, AR245:5, AR177:5, AR060:5, AR257:5, AR252:5, AR255:5, AR231:5, AR246:5, AR296:5, AR212:5, AR217:5, AR195:5, AR205:5, AR179:5, AR263:4, AR274:4, AR275:4, AR247:4, AR227:4, AR290:4, AR312:4, AR300:4, AR033:4, AR232:4, AR104:4, AR262:4, AR242:4, AR190:4, AR264:4, AR313:4, AR293:4, AR288:4, AR230:4, AR286:4, AR200:4, AR213:4, AR225:4, AR236:4, AR283:4, AR089:3, AR316:3, AR308:3, AR039:3, AR287:3, AR240:3, AR172:3, AR175:3, AR297:3, AR199:3, AR294:3, AR174:3, AR285:3, AR189:3, AR196:3, AR299:3, AR168:3, AR203:3, AR185:3, AR295:3, AR096:3, AR311:3, AR234:3, AR191:3, AR282:3, AR188:2, AR277:2, AR223:2, AR224:2, AR258:2, AR171:2, AR173:2, AR218:1, AR235:1, AR169:1 H0265:1 and H0264:1.
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237	HTXJM03	603918	247	AR313:13, AR252:10, AR282:8, AR312:7, AR176:7, AR096:7, AR269:6, AR254:6, AR201:6, AR196:6, AR245:6, AR250:6, AR270:6, AR197:6, AR053:6, AR161:6, AR162:6, AR180:6, AR089:6, AR163:6, AR169:6, AR191:5, AR170:5, AR240:5, AR165:5, AR178:5, AR183:5, AR290:5, AR164:5, AR166:5, AR300:5, AR257:5, AR039:5, AR264:5, AR229:5, AR203:5, AR266:5, AR268:5, AR267:5, AR255:5, AR181:5, AR236:5, AR297:5, AR233:4,

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243	HWADJ89	799506	253	AR252:29, AR250:29, AR253:21, AR254:10, AR282:6, AR215:6, AR165:5, AR164:5, AR166:5, AR089:5, AR161:5, AR246:5, AR162:5, AR271:5, AR240:5, AR053:5, AR163:5, AR263:4, AR243:4, AR274:4, AR195:4, AR205:4, AR313:4, AR096:4, AR299:4, AR180:4, AR213:4, AR193:4, AR214:4, AR169:4, AR300:4, AR311:4, AR264:4, AR192:4, AR173:4, AR207:4, AR312:3, AR285:3, AR171:3, AR309:3, AR060:3, AR275:3, AR308:3, AR196:3, AR272:3, AR316:3, AR269:3, AR257:3, AR261:3, AR170:3, AR270:3, AR183:3, AR242:3, AR245:3, AR296:3, AR199:3, AR287:3, AR295:3, AR175:3, AR033:3, AR172:3, AR222:2, AR188:2, AR039:2, AR185:2, AR290:2, AR286:2, AR247:2, AR238:2, AR191:2, AR297:2, AR178:2, AR268:2, AR291:2, AR262:2, AR200:2, AR235:2, AR104:2, AR283:2, AR212:2, AR210:2, AR288:2, AR203:2, AR201:2, AR174:2, AR277:2, AR182:2, AR197:2, AR189:2, AR255:2, AR294:2, AR229:2, AR230:2, AR293:2, AR258:2, AR216:2, AR236:2, AR224:2, AR181:2, AR190:2, AR239:2, AR228:2, AR227:2, AR233:2, AR234:1, AR177:1, AR231:1, AR179:1, AR061:1, AR266:1, AR055:1, AR226:1, AR221:1, AR289:1, AR232:1 H0581:1
244	HWBCP79	846382	254	AR313:44, AR039:36, AR196:28, AR089:27, AR096:25, AR299:23, AR300:21, AR185:18, AR163:17, AR161:17, AR162:17, AR240:16, AR277:15, AR164:15, AR218:15, AR173:14, AR316:14, AR165:14, AR229:13, AR199:13, AR247:12, AR060:12, AR175:12, AR234:11, AR174:11, AR264:11, AR258:11, AR179:11, AR195:10, AR191:10, AR192:10, AR238:9, AR193:9, AR219:9, AR242:9, AR178:9, AR293:9, AR104:9, AR180:9, AR262:9, AR275:9, AR177:9, AR166:8, AR181:8, AR200:8, AR257:8, AR053:8, AR188:8, AR236:8, AR282:8, AR233:8, AR271:8, AR296:7, AR312:7, AR203:7, AR226:7, AR183:7, AR285:7, AR197:7, AR182:7, AR230:7, AR269:7, AR274:7, AR235:7, AR204:6, AR231:6, AR189:6, AR212:6, AR297:6, AR237:6, AR213:6, AR295:6, AR198:6, AR245:6, AR286:6, AR287:6, AR228:5, AR263:5, AR270:5, AR055:5, AR272:5, AR176:5, AR260:5, AR294:5, AR308:5, AR261:5, AR239:5, AR268:5, AR309:5, AR033:5, AR290:4, AR201:4, AR227:4, AR256:4, AR288:4, AR250:4, AR255:4, AR190:4, AR283:4, AR291:4, AR243:3, AR211:3, AR205:3, AR210:3, AR267:3, AR246:3, AR215:3, AR311:3, AR207:3, AR225:3, AR224:3, AR289:2, AR232:2, AR168:2, AR223:2, AR214:2, AR266:2, AR222:2, AR171:2, AR254:2, AR172:1, AR061:1 H0580:1 and H0169:1.
245	HWBEM18	949402	255	AR225:61, AR169:56, AR223:52, AR170:52, AR168:45, AR215:41, AR171:40, AR214:37, AR243:34, AR296:34, AR254:32, AR266:31, AR222:27, AR291:26, AR246:26, AR224:25, AR289:23, AR172:23, AR221:22, AR297:21, AR253:20, AR216:20, AR217:20, AR245:19, AR213:18, AR183:18, AR250:18, AR288:17, AR205:16, AR179:16, AR295:16, AR283:15, AR270:15, AR039:15, AR256:15, AR193:15, AR255:14, AR269:14, AR178:14, AR285:13, AR096:13, AR197:13, AR271:13, AR235:13, AR261:12, AR316:12, AR195:12, AR242:12, AR180:12, AR268:11, AR260:11, AR192:11, AR176:11, AR089:11, AR267:11, AR181:10, AR212:10, AR173:10, AR293:10, AR182:9, AR163:9, AR262:9, AR161:9, AR162:9, AR287:9, AR240:9, AR201:9, AR165:8, AR247:8, AR164:8, AR204:8, AR207:8, AR166:8, AR294:8, AR286:8, AR237:8, AR236:8, AR198:8, AR290:7, AR238:7, AR282:7, AR104:7, AR312:7, AR313:7, AR311:7, AR033:7, AR299:6, AR272:6, AR309:6, AR257:6, AR308:6, AR060:6,

				AR264:6, AR053:5, AR177:5, AR234:5, AR263:5, AR230:5, AR252:5, AR300:5, AR189:5, AR190:5, AR210:5, AR199:5, AR274:5, AR258:5, AR229:4, AR185:4, AR174:4, AR275:4, AR219:4, AR188:4, AR055:4, AR277:4, AR061:4, AR191:4, AR196:4, AR226:4, AR218:4, AR231:4, AR200:3, AR228:3, AR227:3, AR239:3, AR211:2, AR203:2, AR233:2, AR232:1, H0556:7, H0581:5, H0265:4, H0083:4, H0424:4, H0543:4, H0580:3, H0318:3, L0766:3, L0783:3, H0422:3, H0650:2, L2599:2, H0069:2, H0635:2, H0457:2, H0620:2, H0634:2, L3144:2, L0764:2, L0666:2, L0758:2, H0740:1, H0656:1, H0341:1, L3684:1, H0637:1, H0645:1, H0393:1, L3312:1, H0610:1, H0333:1, H0618:1, H0309:1, H0009:1, H0050:1, H0051:1, H0290:1, H0617:1, S0038:1, S0426:1, H0529:1, L0770:1, L0761:1, L0667:1, L0772:1, L0646:1, L0642:1, L0643:1, L0773:1, L0774:1, L0655:1, L0558:1, L0665:1, H0701:1, L2467:1, L0438:1, L2681:1, H0520:1, H0670:1, H0521:1, H0522:1, H0134:1, L0748:1, L0439:1, L0751:1, L0756:1, H0445:1, S0436:1 and H0216:1.
	HWBEM18	906580	393	
	HWBEM18	877573	394	
246	HWBFX31	799427	256	AR171:3, AR309:2, AR271:2, AR282:2, AR225:2, AR205:2, AR267:2, AR213:2, AR257:2, AR236:2, AR053:1, AR266:1, AR179:1, AR199:1, AR270:1, AR214:1, AR181:1, AR240:1, AR247:1, AR277:1, L0659:5, L0794:4, L0809:4, L0777:4, H0424:3, L0766:3, L0745:3, H0265:2, H0656:2, H0254:2, H0662:2, S0376:2, H0457:2, H0024:2, L0768:2, H0670:2, H0555:2, L0751:2, L0780:2, H0556:1, H0218:1, H0224:1, H0638:1, S0360:1, H0675:1, S0408:1, H0580:1, H0586:1, H0575:1, H0545:1, H0050:1, H0188:1, H0252:1, H0039:1, H0617:1, H0316:1, H0063:1, H0087:1, H0264:1, H0272:1, H0652:1, S0002:1, S0426:1, L0763:1, L0770:1, L0761:1, L0800:1, L0773:1, L0648:1, L0662:1, L0774:1, L0784:1, L0647:1, L0790:1, L0666:1, L0664:1, L0665:1, L0438:1, H0521:1, H0522:1, L0749:1, L0750:1, L0752:1, L0757:1, L0759:1, L0596:1, H0422:1, S0458:1 and H0677:1.
247	HWHGZ51	886212	257	AR283:18, AR089:18, AR316:16, AR282:16, AR060:15, AR277:15, AR104:13, AR202:13, AR246:12, AR241:12, AR281:11, AR194:11, AR240:11, AR055:11, AR096:10, AR299:10, AR039:10, AR219:9, AR206:9, AR218:9, AR205:8, AR313:8, AR315:8, AR185:8, AR243:7, AR204:7, AR300:7, AR265:6, AR280:6, AR192:6, AR263:6, AR244:6, AR271:5, AR198:5, AR266:5, AR247:5, AR289:5, AR284:5, AR285:5, AR314:5, AR295:5, AR273:5, AR296:4, AR291:4, AR310:4, AR213:4, AR182:4, AR232:4, AR269:4, AR183:4, AR275:4, AR294:4, AR267:3, AR033:3, AR177:3, AR312:3, AR268:3, AR298:3, AR270:3, AR229:3, AR286:3, AR184:3, AR309:3, AR238:3, AR175:3, AR053:3, AR227:3, AR234:3, AR274:3, AR052:3, AR290:3, AR231:3, AR186:2, AR293:2, AR237:2, AR251:2, AR226:2, AR292:2, AR248:2, AR256:2, AR233:2, AR259:2, AR258:2, AR253:2, AR061:2, AR179:1, S0132:8, L2522:8, H0264:8, H0586:7, L0747:6, S0476:5, S0330:5, L0755:5, L0751:4, L0581:4, L5623:3, H0188:2, H0031:2, H0494:2, L0776:2, L0809:2, H0696:2, L0731:2, H0556:1, H0295:1, H0177:1, H0638:1, H0370:1, H0592:1, H0587:1, H0486:1, L2539:1, L0021:1, H0081:1, H0271:1, H0181:1, H0617:1, H0380:1, L0653:1, L0659:1, L0783:1, L5622:1, L0789:1, L0791:1, S0328:1, L0752:1, L0601:1 and L3603:1.
248	HWTBK81	460568	258	AR162:6, AR161:6, AR163:6, AR221:6, AR309:5, AR272:4, AR263:4, AR183:4, AR252:4, AR182:4, AR225:4, AR168:4, AR170:4, AR178:3, AR269:3, AR181:3, AR275:3, AR245:3, AR197:3, AR311:3, AR235:3, AR165:3, AR285:3, AR282:3, AR257:3, AR228:3, AR233:3, AR164:3, AR180:3, AR288:3, AR174:3, AR229:3, AR268:3, AR166:3, AR175:3, AR214:3, AR176:3, AR236:3, AR055:2, AR266:2, AR169:2, AR299:2, AR177:2, AR255:2,

				AR240:2, AR226:2, AR089:2, AR239:2, AR287:2, AR185:2, AR237:2, AR238:2, AR061:2, AR231:2, AR216:2, AR179:2, AR293:2, AR060:2, AR316:2, AR277:2, AR191:2, AR193:2, AR313:2, AR230:2, AR217:2, AR196:2, AR261:2, AR289:2, AR290:2, AR297:2, AR200:2, AR188:2, AR271:2, AR234:2, AR247:2, AR205:2, AR207:2, AR262:2, AR190:2, AR172:2, AR312:2, AR227:2, AR291:2, AR223:2, AR189:2, AR201:2, AR267:1, AR171:1, AR104:1, AR096:1, AR204:1, AR294:1, AR258:1, AR246:1, AR300:1, AR250:1, AR199:1, AR033:1 L0439:4, L0748:2, H0351:1, S0364:1, L0768:1, L0650:1, L0375:1, L0747:1 and H0352:1.
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**Table 1C** summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID:), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID:", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

**Table 1C**

<b>cDNA Clone ID</b>	<b>SEQ ID NO:X</b>	<b>CONTIG ID:</b>	<b>BAC ID: A</b>	<b>SEQ ID NO:B</b>	<b>EXON From-To</b>
HAUAI83	30	639009	AC010422	781	1-326 1552-2084 2162-2261 2300-2427 4485-5868 5948-6362 7914-8017 8569-8681 8765-8875 8968-9037 9284-9499 9742-9910 10837-11187 11271-11321 11554-11707 11783-12766 12866-13225 13256-13827 14284-14367 14890-15090
HAUAI83	30	639009	AC018761	782	1-326 1176-1284 1552-2084 2162-2261 2300-2426 4485-5868 5948-6362 8569-8681



					8765-8875 8968-9037 9284-9499 9742-9910 10317-10501 10837-11187 11271-11321 11554-11707 11783-12766 12866-13225 13256-13827 14284-14367 14890-15090
HAUAI83	30	639009	AC010422	783	1-315 2004-2289 2650-2741 3554-3830
HAUAI83	30	639009	AC010422	784	1-202 938-1047 1219-1395 1758-1956 2907-3429 3792-3935 5366-5485 6391-6688 6899-7269 7890-8316 8400-8524 8607-8682 8824-8999 9190-9302 9691-9796 10106-10177 10571-11051 11164-11490 12565-12696 13364-13501 13964-14592 14740-15540 15610-15798 15947-16642 16717-16832 16968-17408 17521-17612 18331-18579 19120-19303 19358-19514 19599-19702 20003-20245
HAUAI83	30	639009	AC018761	785	1-202 938-1047 1219-1395 1758-1956 2907-3429 3792-3935

					5366-5485 6391-6688 6899-7269 7591-7711 7890-8316 8400-8524 8607-8682 8749-9073 9190-9302 9691-9796
HAUA183	30	639009	AC018761	786	1-82 128-293 1178-1447 1986-2278 2457-2711 3543-3844
HBINS58	35	1352386	AL096774	787	1-1023 2010-2239 2581-2962 3153-3223 3324-3493 3973-4126
HBINS58	35	1352386	AL096774	788	1-341
HBINS58	35	1352386	AL096774	789	1-142
HCE3G69	40	728432	AC068946	790	1-108 1186-1324 1746-1835 2138-2284 2448-2545 2718-2861 3091-5889
HCE3G69	40	728432	AC068946	791	1-191
HCE3G69	40	728432	AC068946	792	1-686
HCEFB80	42	1143407	AL022327	793	1-2271 3506-3658 4643-4810 9039-9164 9382-9509 10587-10720 11135-11195 11265-11716 14644-15466 17451-17526 18012-18114 20530-20632 20957-21009 23696-23785 25338-25575 25969-26166
HCNDR47	47	1016919	AL122003	794	1-236 531-696 787-817 863-4508 5158-5744

					6949-7029
HCNDR47	47	1016919	AL122003	795	1-888 1304-2003 2830-3284 3719-4571 4618-5268 6131-6557 8947-9033 9058-9726 14176-14480 18456-18915 18960-19871 22365-22454 23082-23248 28058-28215
HDPGT01	61	771583	AC020978	796	1-180 2776-2899 3916-4077 4296-4335 4436-4632 4895-5181 8153-8246 9547-9666 9907-10007 10370-10618 10788-11046 11926-13423 13465-13494 13764-15689
HDPGT01	61	771583	AC020978	797	1-384
HDPSB18	67	1043263	AL355512	798	1-2572 3049-3871
HDPSB18	67	1043263	AC006176	799	1-2571 3048-3872
HDPSB18	67	1043263	AL355512	800	1-280
HDPXY01	74	879048	AL354000	801	1-1319 4848-4975 5229-5600 6561-6654
HDPXY01	74	879048	AL035362	802	1-1316 4844-4971 5225-5596 6557-6650
HDPXY01	74	879048	AL354000	803	1-460
HDPXY01	74	879048	AL354000	804	1-400
HDPXY01	74	879048	AL035362	805	1-400
HDPXY01	74	879048	AL035362	806	1-460
HFIIN69	93	1011487	AC027797	807	1-1438
HFIIN69	93	1011487	AC027797	808	1-329
HHBCS39	104	1003028	AL390960	809	1-2979
HHBCS39	104	1003028	AL358992	810	1-2983
HHBCS39	104	1003028	AL358992	811	1-207
HHGCG53	110	340818	AC024037	812	1-518
HHGCM76	111	662329	AC003665	813	1-70

					304-609 900-1090 1240-1835 2272-2490 2581-3598
HHGCM76	111	662329	AC003665	814	1-580 851-995 1224-1296 1314-1663 1930-1975 2724-2905 2968-3098 3283-3328 5121-5230 5331-5689
HJACG30	116	895505	AC018512	815	1-776
HJACG30	116	895505	AC022305	816	1-878
HJACG30	116	895505	AC002518	817	1-150
HLTIP94	137	1087335	AC007431	818	1-1299
HLTIP94	137	1087335	AC007431	819	1-330
HMSDL37	154	973996	AC012086	820	1-3328
HMSDL37	154	973996	AC018811	821	1-3051
HMSDL37	154	973996	AC018494	822	1-3029
HMSDL37	154	973996	AC012086	823	1-224
HMSDL37	154	973996	AC012086	824	1-468
HMSDL37	154	973996	AC018811	825	1-222
HMSDL37	154	973996	AC018811	826	1-468
HMSDL37	154	973996	AC018494	827	1-224
HMSDL37	154	973996	AC018494	828	1-1854
HNGOI12	172	1041375	AC003675	829	1-2128
HNGOI12	172	1041375	AC001228	830	1-2129
HNGOI12	172	1041375	AC013791	831	1-2132
HNHFM14	174	664507	AC020552	832	1-290
HNHFM14	174	664507	AC020552	833	1-96
HNTSY18	183	1041383	AC004877	834	1-175 342-474 573-1883 2536-2632 2831-2894 2999-3231 5032-5164 6664-6820 7288-7881
HNTSY18	183	1041383	AC004877	835	1-42 1197-1333 1575-1698 1936-1984 2246-2304
HOHBY44	189	873264	AC074201	836	1-5280 5527-5989 7392-7421
HOHBY44	189	873264	AC074201	837	1-298
HPJBK12	197	1011467	AC022033	838	1-2649
HPJBK12	197	1011467	AC013541	839	1-2649

HPJBK12	197	1011467	AC022033	840	1-190
HPJBK12	197	1011467	AC013541	841	1-190
HPJCL22	198	1146674	AC037447	842	1-102 373-826 995-1315 1450-1567 2189-2515 2599-2778 3138-4132 4537-4681 4864-4998 5144-5324 5394-6211 6816-6941 7472-7647 7791-8885 9056-9368 9506-9733 9799-10100 10277-10988 11213-11751 11783-11838 11875-12474 12592-13077
HPJCL22	198	1146674	AC022400	843	1-102 373-826 995-1315 1450-1567 2189-2515 2599-2778 3138-4132 4537-4681 4864-4998 5144-5324 5394-6211 6816-6941 7472-7647 7791-8885 9056-9368 9506-9733 9799-10100 10277-10988 11213-11751 11783-11837 11874-12473 12591-13076
HPJCL22	198	1146674	AC037447	844	1-207
HPJCL22	198	1146674	AC037447	845	1-2124
HPJCL22	198	1146674	AC022400	846	1-207
HPJCL22	198	1146674	AC022400	847	1-2124 2470-2567 2865-2971
HPRAL78	200	1352342	AC007783	848	1-2334 2508-3084

					3578-3890 4198-4294 4376-4623 4712-5349 5369-6088 6527-7107 7298-7392 7730-7846 9147-9476 10487-10575 10791-11298 11485-11601 11783-13009 13207-13501 13540-13772 14439-14800 14923-14983 15133-15355 15485-15653 16750-16805 16894-17078 17162-17219 18003-18089 21085-21146 21358-21501
HPRAL78	200	1352342	AC007783	849	1-308
HPRAL78	200	1352342	AC007783	850	1-1024
HRGBL78	204	910133	AL359541	851	1-254 2777-3307 3670-3823 4113-4385 4844-5381 5995-7365
HSAWD74	207	460527	AC004951	852	1-1651 1740-2593
HSAWD74	207	460527	AC004951	853	1-149
HSAWD74	207	460527	AC004951	854	1-5057 5082-8353 8404-8996
HTPCS72	240	854941	AL008639	855	1-106 1457-1595 1666-2484 2910-3006 3705-4147 4768-5141 5304-5536 5746-5874 7114-7241 7468-7711 7963-8746 9438-12408 12884-14976
HTPCS72	240	854941	AL008639	856	1-720
HTPIH83	241	919916	AL158821	857	1-1862

**Table 1D:** The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

The present invention encompasses methods of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating diabetes mellitus comprising administering to a patient in which such detection, treatment, prevention, and/or amelioration is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate diabetes mellitus.

In another embodiment, the present invention also encompasses methods of detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; comprising administering to a patient combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in Column 3 of Table 1D.

Table 1D provides information related to biological activities for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information related to assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA Clone ID:") provides the unique clone identifier for each clone as previously described and indicated in Table 1A through Table 1D. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Tables 1A, Table 1B, and Table 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity.

Table 1D describes the use of, inter alia, FMAT technology for testing or demonstrating various biological activities. Fluorometric microvolume assay technology (FMAT)

is a fluorescence-based system which provides a means to perform nonradioactive cell- and bead-based assays to detect activation of cell signal transduction pathways. This technology was designed specifically for ligand binding and immunological assays. Using this technology, fluorescent cells or beads at the bottom of the well are detected as localized areas of concentrated fluorescence using a data processing system. Unbound fluorophore comprising the background signal is ignored, allowing for a wide variety of homogeneous assays. FMAT technology may be used for peptide ligand binding assays, immunofluorescence, apoptosis, cytotoxicity, and bead-based immunocapture assays. See, Miraglia S et. al., "Homogeneous cell and bead based assays for highthroughput screening using fluorometric microvolume assay technology," *Journal of Biomolecular Screening*; 4:193-204 (1999). In particular, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides (including polypeptide fragments and variants) to activate signal transduction pathways. For example, FMAT technology may be used to test, confirm, and/or identify the ability of polypeptides to upregulate production of immunomodulatory proteins (such as, for example, interleukins, GM-CSF, Rantes, and Tumor Necrosis factors, as well as other cellular regulators (e.g. insulin)).

Table 1D also describes the use of kinase assays for testing, demonstrating, or quantifying biological activity. In this regard, the phosphorylation and de-phosphorylation of specific amino acid residues (e.g. Tyrosine, Serine, Threonine) on cell-signal transduction proteins provides a fast, reversible means for activation and de-activation of cellular signal transduction pathways. Moreover, cell signal transduction via phosphorylation/de-phosphorylation is crucial to the regulation of a wide variety of cellular processes (e.g. proliferation, differentiation, migration, apoptosis, etc.). Accordingly, kinase assays provide a powerful tool useful for testing, confirming, and/or identifying polypeptides (including polypeptide fragments and variants) that mediate cell signal transduction events via protein phosphorylation. See e.g., Forrer, P., Tamaskovic R., and Jaussi, R. "Enzyme-Linked Immunosorbent Assay for Measurement of JNK, ERK, and p38 Kinase Activities" *Biol. Chem.* 379(8-9): 1101-1110 (1998).



Table 1D

Gene No.	cDNA Clone ID	AA SEQ ID NO: Y	Biological Activity	Exemplary Activity Assay	Preferred Indication
1	H2CBU83	405	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious</p>

				<p>available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
2	H6EDC19	406	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN,</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>

				<p>et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17711-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
2	H6EDC19	406	Proliferation of pre-adipose cells (such as 3T3-L1 cells)	<p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo<sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to</p>	

				<p>measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.</p>	
3	HACBD91	407	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic</p>

				<p>response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
3	HACBD91	407	<p>Activation of transcription through cAMP response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of</p>	<p>Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and</p>

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transgene expression through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.</p>	<p>infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL),</p>
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					<p>plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p>
3	HACBD91	407	Production of IL-6	<p>IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-</p>

				<p>immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred</p>
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3	HACBD91	407	Regulation of transcription of Malic Enzyme in adipocytes	<p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also respond to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988);</p>	<p>indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially</p>
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				and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
3	HACBD91	407	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys	A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating

				<p>Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>(e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) the activation of and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly</p>
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					<p>preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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				<p>and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred</p>
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				indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
3	HACBD91	407	<p>Activation of transcription through CD28 response element in immune cells (such as T-cells).</p> <p>Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the</p>

				<p>Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.</p>	<p>invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. An additional highly preferred indication includes infection (e.g., AIDS, and/or as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma (e.g., metastatic melanoma), renal cell carcinoma (e.g., metastatic renal cell carcinoma), leukemia, lymphoma (e.g., T cell lymphoma), and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for</p>
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			killer cells).	<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic</p>	<p>Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma,</p>
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				activity.	Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
3	HACBD91	407	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of	A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred

				<p>each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below</p>
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3	HACBD91	407	<p>Activation of transcription through API response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the API response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and</p>	<p>under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma,</p>
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				IL-4 responsive suspension-culture cell line.	AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.
3	HACBD91	407	Activation of transcription through CD28 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol	<p>A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune</p>

				<p>Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Highly preferred indications include neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma (e.g., metastatic melanoma), renal cell carcinoma (e.g., metastatic renal cell carcinoma), leukemia, lymphoma (e.g., T cell lymphoma), and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. A highly preferred indication includes infection (e.g., AIDS, tuberculosis, infections associated with granulomatous disease, and osteoporosis, and/or as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred</p>
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					indications include suppression of immune reactions to transplanted organs and/or tissues, uveitis, psoriasis, and tropical spastic paraparesis. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
3	HACBD91	407	Activation of transcription through NFAT response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or	Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly

				<p>routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
	HACBD91	407	Activation of	Assays for the activation of	Highly preferred indications



3	transcription through NFKB response element in immune cells (such as T-cells).	transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.	include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia,
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					thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.
3	HACBD91	407	Activation of transcription through STAT6 response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al.,	<p>A highly preferred indication is allergy. Another highly preferred indication is asthma. Additional highly preferred indications include inflammation and inflammatory disorders.</p> <p>Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders").</p> <p>Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).</p> <p>Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include</p>

				<p>Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curjel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
4	HACCI17	408	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for</p>

				<p>invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p>
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					<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications</p>
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					<p>associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
4	HACCI17	408	Production of IL-8 by immune cells (such as the human EOL-1 eosinophil cells)	Assay that measures the production of the chemokine interleukin-8 (IL-8) from immune cells (such as the EOL-1 human eosinophil cell line) are well	Highly preferred indications include eosinophilia, asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory

				known in the art (for example, measurement of IL-8 production by FMA <sup>T</sup> ) and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit. Eosinophils are a type of immune cell important in allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. IL8 is a strong immunomodulator and may have a potential proinflammatory role in immunological diseases and disorders (such as allergy and asthma).	disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting or inhibiting immune cell proliferation. Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include boosting an eosinophil-mediated immune response, and suppressing an eosinophil-mediated immune response.
4	HACCI17	408	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to	Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g.,

				<p>regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature</p>	<p>rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
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4	HACCI17	408	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>mast cells.</p> <p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute</p>
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4	HACCI17	408		<p>Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
			Production of IL-5	<p>IL-5 FMAT. Assays for immunomodulatory proteins secreted by TH2 cells, mast cells, basophils, and eosinophils that stimulate eosinophil function and B cell Ig production and promote polarization of CD4+ cells into TH2 cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, stimulate immune cell function, modulate B cell Ig production, modulate immune cell polarization, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate</p>	<p>A highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-5 production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-5 production. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) immunoglobulin production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) immunoglobulin production. A highly preferred indication includes allergy. A highly preferred indication includes asthma. A highly preferred indication includes</p>

				<p>the production of cytokines, such as IL-5, and the stimulation of eosinophil function and B cell Ig production. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Ohshima et al., Blood 92(9):3338-3345 (1998); Jung et al., Eur J Immunol 25(8):2413-2416 (1995); Mori et al., J Allergy Clin Immunol 106(1 Pt 2):558-564 (2000); and Koning et al., Cytokine 9(6):427-436 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>rhinitis. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL),</p>
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4	HACCI17	408	Production of ICAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Endothelial cells, which are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used in ICAM production assays include human umbilical vein endothelial cells (HUVEC), and are available from commercial sources. The expression of ICAM (CD54), a integral membrane protein, can be upregulated by cytokines or other factors, and ICAM expression is important in mediating immune and endothelial cell interactions leading to immune and inflammatory responses. Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that	plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
				Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.	

				may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety.	
4	HACCI17	408	Production of IL-8 by endothelial cells (such as Human Umbilical Cord Endothelial Cells).	<p>Assays measuring production of IL-8 are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8. For example, FMAT may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8 from endothelial cells (such as human umbilical vein endothelial cells (HUVEC)). HUVECs are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Endothelial cells play a pivotal role</p> <p>Highly preferred indications include immunological and inflammatory disorders (e.g., such as allergy, asthma, leukemia, etc. and as described below under "Immune Activity", and "Blood-Related Disorders"). Highly preferred indications also include autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), neoplastic disorders (e.g., organ cancers such as lung, liver, colon cancer, and/or as described below under "Hyperproliferative Disorders"), and cardiovascular disorders (e.g., such as described below under "Cardiovascular Disorders"). Preferred indications include thrombosis, bacteremia and sepsis syndrome and consequent complications (such as acute respiratory distress syndrome and systemic ischemia-reperfusion</p>	

4	HACCI17	408	Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>in the initiation and perpetuation of inflammation and secretion of IL-8 may play an important role in recruitment and activation of immune cells such as neutrophils, macrophages, and lymphocytes.</p> <p>RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp</p>	resulting from septic shock), restnosis and atherosclerosis.
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4	HACCI17	408	<p>Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred</p>
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				are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.	indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
5	HAGAQ26	409	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett. 377(2):237-9	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the



				<p>(1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
6	HAGDS35	410	<p>Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes</p>	<p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental</p>

			<p>transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an</p>	<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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7	HAGFI62	411	Activation of Adipocyte ERK Signaling Pathway	adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as</p>
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				<p>incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>
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					<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as,</p>
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8	HAHDB16	412	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999);</p>	<p>lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine</p>
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				<p>Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel</p>
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					<p>blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones,</p>
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8	HAHDB16	412	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the	<p>osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>
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				transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.
8	HAHDB16	412	Production of IFNgamma using a T	IFNgamma FMAT. IFNγ plays a central role in the immune system	A highly preferred embodiment of the invention includes a method

			cells	<p>and is considered to be a proinflammatory cytokine. IFN<math>\gamma</math> promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFN<math>\gamma</math>), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach"</p>	<p>for stimulating the production of IFN<math>\gamma</math>. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFN<math>\gamma</math>. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for</p>
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				<p>Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
9	HAICP19	413	<p>Activation of Adipocyte P13 Kinase Signalling Pathway</p>	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for P13 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for P13 kinase</p>	<p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting</p>

				<p>activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy</p>
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					<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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9	HAICP19	413	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure	<p>associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders.</p> <p>Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer.</p> <p>Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Vascular Disease, Atherosclerosis, Restenosis, Stroke, and Asthma.</p>
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				<p>ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include Aortic Smooth Muscle Cells (AOSMC); such as bovine AOSMC.</p>	
9	HAICP19	413	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred</p>



				transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.	indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
9	HAICP19	413	Activation of Natural Killer Cell ERK Signaling Pathway.	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate	A highly preferred embodiment of the invention includes a method for stimulating natural killer cell

			<p>cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary natural killer cells that may be used according to these assays include the human natural killer cell lines (for example, NK-YT cells which have cytolytic and cytotoxic activity) or primary NK cells.</p>	<p>proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting natural killer cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating natural killer cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting natural killer cell differentiation. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity") and infections (e.g., as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory</p>
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					disorders. Highly preferred indications also include cancers such as, kidney, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary cancer, lymphoma and leukemias. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Other highly preferred indications include, pancytopenia, leukopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), arthritis, asthma, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, immune reactions to transplanted organs and tissues, endocarditis, meningitis, Lyme Disease, and allergies.
10	HAIFL18	414	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease</p>
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					<p>(e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin</p>
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10	HAIFL18	414	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins	<p>resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating the production of IFNg. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNg. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-</p>
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				<p>produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein</p>	<p>Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example,</p>
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				<p>hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
			<p>incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and</p>
			<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998);</p>	
			<p>Activation of transcription through serum response element in immune cells (such as natural killer cells).</p>	



				<p>Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues,</p>
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11	HAIJAN23	415	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 (Pt 3):847-51	hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").  A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy
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				<p>(1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec; 10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
12	HAJBR69	416	<p>Regulation of transcription through the PEPCK promoter in hepatocytes</p>	<p>Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>

				<p>may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p>
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					<p>Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-</p>
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12	HBJBR69	416	Production of GM-CSF	<p>GM-CSF FMAT. GM-CSF is expressed by activated T cells, macrophages, endothelial cells, and fibroblasts. GM-CSF regulates differentiation and proliferation of granulocytes- macrophage progenitors and enhances antimicrobial activity in neutrophils, monocytes and macrophage. Additionally, GM-CSF plays an important role in the differentiation of dendritic cells and monocytes, and increases antigen presentation. GM-CSF is considered to be a proinflammatory cytokine. Assays for immunomodulatory proteins that promote the production of GM-CSF are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and modulate the growth and differentiation of leukocytes. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as GM-CSF, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating the production of GM-CSF. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of GM-CSF. Highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., as described below under "Infectious Disease".</p> <p>Highly preferred indications include blood disorders (e.g., neutropenia (and the prevention of neutropenia (e.g., in HIV infected patients), and/or as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include asthma. Highly preferred indications include neoplastic diseases (e.g., leukemia (e.g., acute lymphoblastic leukemia, and acute myelogenous leukemia), lymphoma (e.g., non-Hodgkin's lymphoma and</p>
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			<p>antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Ye et al., J Leukoc Biol (58(2):225-233, the contents of each of which are herein incorporated by reference in its entirety. Natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC) or may be isolated using techniques disclosed herein or otherwise known in the art. Natural killer (NK) cells are large granular lymphocytes that have cytotoxic activity but do not bind antigen. NK cells show antibody-independent killing of tumor cells and also recognize antibody bound on target cells, via NK Fc receptors, leading to cell-mediated cytotoxicity.</p>	<p>Hodgkin's disease), and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications include: suppression of immune reactions to transplanted organs and tissues (e.g., bone marrow transplant); accelerating myeloid recovery; and mobilizing hematopoietic progenitor cells. Preferred indications include boosting a T cell-mediated immune response, and alternatively, suppressing a T cell-mediated immune response. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and allergy.</p>
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13	HAMFE15	417	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	<p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the</p> <p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications</p>
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				<p>human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
14	HAMGR28	418	<p>Stimulation of Calcium Flux in pancreatic beta cells.</p>	<p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>

				<p>factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATCC# CRL-1777 Refs: Lord and</p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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15	HAPBS03	419	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel</p>
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				<p>mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine</p>
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					<p>disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach,</p>
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				<p>incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>
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					<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as,</p>
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				<p>(2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
18	HAPUC89	422	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the</p>

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic neuropathy, kidney disease</p>
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					<p>(e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin</p>
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					<p>resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
18	HAPUC89	422	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune</p>

				<p>and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line,</p>	<p>Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
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18	HAPUC89	422	Activation of Skeletal Muscle Cell ERK Signalling Pathway	<p>which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>Kinase assay. Kinase assays, for example Elk-1 kinase assays, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may</p>	<p>Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders") and disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage</p>
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				<p>be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including</p>
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19	HATBR65	423	Production of IL-6	<p>IL-6 FMT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly</p>	<p>myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Highly preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and</p>
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				<p>regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., <i>J Biomolecular Screening</i> 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., <i>J Immunol</i> 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human</p>	<p>infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia,</p>
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19	HATBR65	423		<p>dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
			<p>Regulation of Malic Enzyme in adipocytes</p>	<p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements. MEp and MEd identified as putative PPAR response elements. ME promoter may also respond to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and</p>

			<p>invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.</p>	<p>disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
20	HAUAI83	424	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and</p> <p>Insulin Secretion</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>

				<p>disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT T15 Cells. HIT T15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATCC# CRL-1777</p> <p>Refs: Lord and Ashcroft. <i>Biochem.</i></p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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21	HBAMB15	425	Stimulation of insulin secretion from pancreatic beta cells.	<p>J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC)</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially</p>
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				and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Afari et al. Endocrinology 1992 130:167.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
22	HBGBA69	426	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section

23	HBGNU56	427	<p>Activation of Hepatocyte ERK Signaling Pathway</p>	<p>(2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell differentiation. A</p>
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				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat liver hepatoma cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat liver hepatoma cells that may be used according to these assays include H4Ile cells, which are known to respond to glucocorticoids, insulin, or cAMP derivatives.</p>	<p>highly preferred embodiment of the invention includes a method for activating hepatocyte cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating hepatocyte cells. Highly preferred indications include disorders of the liver and/or endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage</p>
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					<p>(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including</p>
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24	HBIAE26	428	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMA T using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in</p>	<p>myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hepatitis, jaundice, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism. Additional highly preferred indications include neoplasms and cancers, such as, hepatocarcinomas, other liver cancers, and colon and pancreatic cancer. Preferred indications also include prostate, breast, lung, esophageal, stomach, brain, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>
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				<p>diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc.</p>	<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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26	HBIFU48	430	Activation of Adipocyte ERK Signaling Pathway	<p>Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK or kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke,</p>
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				<p>used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>
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					<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer.</p>
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26	HBJFU48	430	Production of IL-6	<p>IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and</p>	<p>Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory</p>
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			<p>upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
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27	HBJLC01	431	<p>Activation of Adipocyte PI3 Kinase Signalling Pathway</p>	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo</p>	<p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below</p>
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					<p>a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g.,</p>
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					<p>infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and</p>
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27	HBJLC01	431	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell</p>	<p>pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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					<p>Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
27	HBJLC01	431	<p>Activation of transcription through API response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the API response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly</p>	

27	HBJLC01	431	Production of IL-6	<p>assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.</p>	<p>preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p>
				<p>IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6</p>

				<p>expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol</p>	<p>production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and</p>
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				<p>158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
27	HBJLC01	431	<p>Activation of transcription through STAT6 response element in immune cells (such as mast cells).</p>	<p>Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes.</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include hematopoietic and immunological disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), autoimmune diseases</p>

				<p>Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>(e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include hematopoietic and immunological disorders such as arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
27	HBJLC01	431	Production of RANTES in endothelial cells (such as human umbilical vein	<p>RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well</p>	

			endothelial cells (HUVEC))	known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which	
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28	HBNAW17	432	<p>Activation of transcription through serum response element in immune cells (such as T-cells).</p>	<p>are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia,</p>
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				<p>may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays</p>	<p>highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with</p>
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29	HCE2F54	433		<p>include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
			<p>Regulation of transcription through the PEPCK promoter in hepatocytes</p>	<p>Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>

				<p>USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas. Highly preferred indications include</p>
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					<p>blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
29	HCE2F54	433	<p>Activation of transcription through NFKB response element in epithelial cells (such as HELA cells).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Cancer, Wound Healing, and Inflammation. Highly</p>

				<p>antagonists of the invention) to regulate NFkB transcription factors and modulate expression of epithelial genes. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Kaltschmidt B, et al., Oncogene, 18(21):3213-3225 (1999); Beetz A, et al., Int J Radiat Biol, 76(11):1443-1453 (2000); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Epithelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary epithelial cells that may be used according to these assays include the HELA cell line.</p>	<p>preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include inflammation and inflammatory disorders.</p>
	HCE2F54	433	Inhibition of squalene synthetase gene transcription.	<p>Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol</p>	

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29	HCE2F54	433			<p>biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.</p> <p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo<sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state</p>	
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29	HCE2F54	433	Activation or inhibition of transcription through NFkB response element in immune cells (such as basophils).	<p>before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.</p> <p>This reporter assay measures activation or inhibition of the NFkB signaling pathway in Ku812 human basophil cell line. Assays for the activation or inhibition of transcription through the NFkB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFkB transcription factors and modulate expression of immunomodulatory genes. NFkB is important in the pathogenesis of asthma. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which</p>	
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29	HCE2F54	433	<p>Activation of transcription through NFKB response element in immune cells (such as the U937 human monocyte cell line).</p>	<p>This assay uses a NFKB response element (which will bind NFKB transcription factors) linked to a reporter gene to measure NFKB mediated transcription in the human monocyte cell line U937. NFKB is upregulated by cytokines and other factors and NFKB element activation leads to expression of immunomodulatory genes. Activation of NFKB in monocytes can play a role in immune responses. Exemplary assays for transcription through the NFKB response element</p>	<p>are herein incorporated by reference in its entirety. Cells were pretreated with SID supernatants or controls for 15-18 hours, and then 10 ng/mL of TNF was added to stimulate the NFKB reporter. SEAP activity was measured after 48 hours. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils. See, Kishi et al., Leuk Res. 9:381-390 (1985); Blom et al., Eur J Immunol. 22:2025-32 (1992), where the contents of each are herein incorporated by reference in its entirety.</p>	<p>Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies</p>
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				<p>that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Monocytic cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human monocyte cells that may be used according to these assays include the U937 cell line, which is cell line derived by Sundstrom and Nilsson in 1974 from malignant cells obtained from the pleural effusion of a patient with histiocytic lymphoma.</p>	<p>(e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>
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30	HCE3G69	434	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	
30	HCE3G69	434	Proliferation of pre-adipose cells (such as 3T3-L1 cells)	Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo <sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a	

				continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.	
30	HCE3G69	434	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening,	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision



			<p>4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
30	HCE3G69	434	<p>Production of IL-10 and activation of T-cells.</p>	<p>Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson,</p> <p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.</p>

				<p>DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology &amp; Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.</p>	
31	HCE5F43	435	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>

			<p>disregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4: 193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
32	HCEFB80	436	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS)</p>	<p>Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as</p>

			<p>in immune cells (such as T-cells).</p>	<p>response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.</p>	<p>described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and</p>
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					<p>malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p>
32	HCEFB80	436	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma,</p>

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
33	HCENK38	437	Protection from Endothelial Cell	Caspase Apoptosis Rescue. Assays for caspase apoptosis rescue are well	A highly preferred embodiment of the invention includes a method for

		Apoptosis.	<p>known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to inhibit caspase protease-mediated apoptosis. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis rescue of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Romeo et al., Cardiovasc Res 45(3): 788-794 (2000); Messmer et al., Br J Pharmacol 127(7): 1633-1640 (1999); and J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An</p>
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					<p>alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders").</p> <p>Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid</p>
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					<p>tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury</p>
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					<p>such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and</p>
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33	HCENK38	437	<p>Activation of transcription through GAS response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T</p>	<p>Crohn's disease), and pain management.</p> <p>Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related</p>
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				cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.	Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
33	HCENK38	437	Activation of Hepatocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used	A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell differentiation. An alternative highly preferred embodiment of the invention

				<p>or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat liver hepatoma cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat liver hepatoma cells that may be used according to these assays include H4Ile cells, which are known to respond to glucocorticoids, insulin, or cAMP derivatives.</p>	<p>includes a method for inhibiting hepatocyte cell differentiation. A highly preferred embodiment of the invention includes a method for activating hepatocyte cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating hepatocyte cells. Highly preferred indications include disorders of the liver and/or endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>
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					<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred</p>
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					<p>indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include, hepatitis, jaundice, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism.</p> <p>Additional highly preferred indications include neoplasms and cancers, such as, hepatocarcinomas, other liver cancers, and colon and pancreatic cancer. Preferred indications also include prostate, breast, lung, esophageal, stomach, brain, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
34	HCEWE20	438	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin.	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p>

				<p>ME promoter contains two direct repeat (DR1)-like elements. MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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34	HCEWE20	438	Production of ICAM-1	<p>isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p> <p>Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include Aortic Smooth Muscle Cells (AOSMC); such as bovine AOSMC.</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Vascular Disease, Atherosclerosis, Restenosis, Stroke, and Asthma.</p>
36	HCGMD59	440	Inhibition of adipocyte ERK signaling pathway.	<p>Kinase assay: measures the phosphorylation of Elk-1, an indication of activation of extracellular signal regulated kinase (ERK). ERK pathway regulates cell</p>	

36	HCGMD59	440	Insulin Secretion	<p>growth, proliferation and differentiation. Cells were pretreated with SID supernatants for 15-18 hours, and then 100 nM of insulin was added to stimulate ERK kinase. Phosphorylation of Elk-1 was measured after a 20 minute incubation. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art. Cells were differentiated to an adipose-like state before being used in the screen. See Green et al., Cell 3: 127-133 (1974), the contents of which are herein incorporated by reference in its entirety.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>
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				<p>using anti-rat insulin antibodies.</p> <p>Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is</p>	<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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37	HCNDR47	441	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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37	HCNDR47	441	Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
				RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used or routinely modified to test immunomodulatory activity of	

38	HCNSB61	442	Activation of Adipocyte ERK Signaling Pathway	<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred</p>
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				<p>differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional</p>
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					highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include
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weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.					
<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth.</p> <p>An alternative highly preferred embodiment of the invention includes a method for inhibiting</p>	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or</p>	Endothelial Cell Apoptosis	442	HCNSB61	38

				<p>antagonists of the invention) to promote caspase protease-mediated apoptosis. Induction of apoptosis in endothelial cells supporting the vasculature of tumors is associated with tumor regression due to loss of tumor blood supply. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis,</p>
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				<p>cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangioepicytoma,</p>
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					<p>lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and</p>
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					coagulative disorders, vasculitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
41	HCUIM65	445	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response	A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"

			<p>element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-</p>	<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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41	HCUM65	445	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic</p>
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				<p>response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
41	HCUIM65	445	<p>Activation of transcription through serum response element in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight</p>



			<p>ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below). Additional highly preferred indications are complications associated with insulin resistance.</p>
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41	HCUIM65	445	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,
41	HCUIM65	445	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by	

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
41	HCUIM65	445	<p>Activation of transcription through GATA-3 response element in immune</p>	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious</p>

			cells (such as mast cells).	<p>cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al.; Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used</p>	<p>disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia,</p>
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				<p>neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
41	HCUIM65	445	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include</p>
				<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative</p>

				assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.	Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
41	HCUIM65	445	Activation of transcription through NFkB response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFkB signaling pathway in HMC-1 human mast cell line. Activation of NFkB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFkB response element are well-known in the art and may be used or routinely	Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as

				<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFκB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFκB response element that may be used or routinely modified to test NFκB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
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41	HCUIM65	445	<p>Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
41	HCUIM65	445	<p>Activation of transcription through NFAT response element in immune cells (such as natural</p>	<p>Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely</p>	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular</p>



			killer cells).	<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic</p>	<p>Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma,</p>
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41	HCUIM65	445	<p>Activation of transcription through NFKB response element in immune cells (such as natural killer cells).</p>	<p>assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Arambourau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844</p>	<p>activity.</p>	<p>Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p> <p>Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and</p>
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				<p>(1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>
41	HCUIM65	445	<p>Activation of transcription through serum response element in immune cells (such as natural killer cells).</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune</p>

				<p>transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia</p>
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41	HCUIM65	445	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and	(ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
				Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus,	

				<p>Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Hentinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).</p>	<p>multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p>
	HCWDS72	446	Regulation of	Assays for the regulation of	A highly preferred indication is

42	transcription of Malic Enzyme in adipocytes	transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements. MEp and MEδ identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its	diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity
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43	HCWKC15	447	<p>Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes</p>	<p>entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.</p> <p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed</p>	<p>and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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				<p>in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
43	HCWKC15	447	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight</p>

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC)</p>	<p>gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly</p>
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				<p>and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>preferred indications are complications associated with insulin resistance.</p>
43	HCWKCI5	447	<p>Activation of transcription through serum response element in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>

43	HCWKCI5	447		<p>which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below). Additional highly preferred indications are complications associated with insulin resistance.</p>
			<p>Activation of transcription through GAS response element in immune cells (such as eosinophils).</p>	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate gene expression (commonly via STAT transcription factors) involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include</p>	<p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting an eosinophil-mediated immune response and, alternatively, suppressing an eosinophil-mediated immune response.</p>

				<p>assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995); the contents of each of which are herein incorporated by reference in its entirety. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate or inhibit activation of immune cells include assays disclosed and/or cited in: Mayumi M., "EoL-1, a human eosinophilic cell line" Leuk Lymphoma; Jun;7(3):243-50 (1992); Bhattacharya S, "Granulocyte macrophage colony-stimulating factor and interleukin-5 activate STAT5 and induce CIS1 mRNA in human peripheral blood eosinophils" Am J Respir Cell Mol Biol; Mar;24(3):312-6 (2001); and, Du J, et al., "Engagement of the CrkL adapter in interleukin-5 signaling in eosinophils" J Biol Chem; Oct 20;275(42):33167-75 (2000); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may</p>
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43	HCWKC15	447	<p>Activation of transcription through NFKB response element in immune cells (such as EOL1 cells).</p>	<p>be used according to these assays include eosinophils. Eosinophils are a type of immune cell important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Increases in GAS mediated transcription in eosinophils is typically a result of STAT activation, normally a direct consequence of interleukin or other cytokine receptor stimulation (e.g. IL3, IL5 or GMCSF).</p>	<p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, and inflammation. Preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), immunological disorders, inflammation and inflammatory disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).</p>
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43	HCWKC15	447	<p>Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFkB element to a reporter gene and binds to the NFkB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils. Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.</p>	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related</p>
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			<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the</p>	<p>Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
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43	HCWKC15	447	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia,</p>
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				<p>(1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
43	HCWKCI5	447	<p>Activation of transcription through NFKB response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the NFKB signaling pathway in HMC-1 human mast cell line. Activation of NFKB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes.</p>	<p>Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below)</p>

				<p>Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
43	HCWKC15	447	<p>Activation of transcription through STAT6 response element in immune cells (such as mast cells).</p>	<p>Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory</p>

			<p>used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with</p>	<p>disorders. Preferred indications also include hematopoietic and immunological disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include hematopoietic and immunological disorders such as arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus,</p>
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43	HCWKC15	447	<p>Activation of transcription through NFKB response element in immune cells (such as basophils).</p>	<p>mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>This reporter assay measures activation of the NFKB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes.</p> <p>Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC).</p>	<p>endocarditis, meningitis, and Lyme Disease.</p> <p>Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
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43	HCWKCI5	447	<p>Activation of transcription through NFAT response element in immune cells (such as natural killer cells).</p>	<p>Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.</p> <p>Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et</p>	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung,</p>
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				<p>al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysplastic disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
43	HCWKC15	447	<p>Activation of transcription through NFKB response element in immune cells (such as natural killer cells).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response</p>	<p>Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional</p>

				<p>element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>	<p>A preferred embodiment of the</p>
HCWKC15	447	Activation of	Assays for the activation of			



43	transcription through serum response element in immune cells (such as natural killer cells).	transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.	invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant
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glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").					
Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include	Assays for the activation of transcription through the NFkB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFkB transcription factors	Activation of transcription through NFkB response element in immune cells (such as natural killer cells).	447	HCWKC15	43

				<p>and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NKL cell line, which is a human natural killer cell line established from the peripheral blood of a patient with large granular lymphocytic leukemia. This IL-2 dependent suspension culture cell line has a morphology resembling that of activated NK cells.</p>	<p>autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia,</p>
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43	HCWKCI5	447	<p>Activation of transcription through API response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the API response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g.,</p>	<p>hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p> <p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-</p>
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43	HCWKC15	447	<p>Activation of transcription through CD28 response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire</p>	<p>through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly</p>
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43	HCWKC15	447	<p>Activation of transcription through GAS response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression</p>	<p>osteoporosis, and/or as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred indications include suppression of immune reactions to transplanted organs and/or tissues, uveitis, psoriasis, and tropical spastic paraparesis. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p> <p>Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate,</p>
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				involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).	breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL),
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					plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
43	HCWKCI5	447	Activation of transcription through NFAT response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000);	Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such

				<p>De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
43	HCWKC15	447	<p>Activation of transcription through NFKB response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element</p>	<p>Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and</p>

				<p>that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs,</p>
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44	HCWUM50	448	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays</p>	<p>asthma and allergy.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below</p>
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				<p>include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>
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					<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include</p>
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				<p>may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and</p>
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					<p>disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional</p>
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					preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
46	HDPBA28	450	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the

				<p>(1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
46	HDPBA28	450	<p>Production of IL-10 and activation of T-cells.</p>	<p>Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation</p>	<p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.</p>

				include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.	
47	HDPBI32	451	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred</p>	

				<p>differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional</p>
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					highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include
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weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.					
A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for P13 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely	Activation of Skeletal Muscle Cell P13 Kinase Signalling Pathway	452	HDPC191	48

				<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune</p>
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					<p>Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders", immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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					<p>wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p> <p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer.</p> <p>Other preferred indications include benign dysproliferative disorders and</p>
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49	HDPCL63	453	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which	pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.  A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hypermolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially
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50	HDPCO25	454	Regulation of viability and proliferation of pancreatic beta cells.	<p>is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p> <p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., <i>Endocrinology</i>, 139(1):172-8 (1998); Krautheim A, et al, <i>Exp Clin Endocrinol Diabetes</i>, 107 (1):29-34</p>	<p>of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>
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				<p>(1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
50	HDP025	454	<p>Activation of transcription through NFKB response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely</p>	<p>Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as</p>

				<p>modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>
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51	HDPGT01	455	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 ( Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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52	HDPHI51	456	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p> <p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B,</p>	<p>highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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				<p>et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
				<p>Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al.,</p>	<p>A highly preferred indication is allergy. Another highly preferred indication is asthma. Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as</p>
52	HDPHI51	456	Activation of transcription through STAT6 response element in immune cells (such as T-cells).		

				<p>Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p> <p>An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for</p>
53	HDPJM30	457	Production of MCP-1	<p>MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be</p>	

				<p>used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting</p>	<p>inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as</p>
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				cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
53	HDPJM30	457	Regulation of transcription through the FAS promoter element in hepatocytes	Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section</p>

				<p>invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
53	HDPJM30	457	<p>Activation or inhibition of transcription through NFKB response element in immune cells (such as basophils).</p>	<p>This reporter assay measures activation or inhibition of the NFKB signaling pathway in Ku812 human basophil cell line. Assays for the activation or inhibition of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. NFKB is important in the pathogenesis of</p>	

				<p>asthma. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Cells were pretreated with SID supernatants or controls for 15-18 hours, and then 10 ng/mL of TNF was added to stimulate the NFkB reporter. SEAP activity was measured after 48 hours. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils. See, Kishi et al., Leuk Res. 9:381-390 (1985); Blom et al., Eur J Immunol. 22:2025-32 (1992), where the contents of each</p>
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54	HDPND46	458	Activation of Adipocyte PI3 Kinase Signalling Pathway	are herein incorporated by reference in its entirety. Kinase assay. Kinase assays, for example an GSK-3 assays, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of	A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or
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				<p>3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>"Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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					<p>and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer.</p>
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54	HDPND46	458	Production of IL-4	<p>IL-4 FMAT. Assays for immunomodulatory proteins secreted by TH2 cells that stimulate B cells, T cells, macrophages and mast cells and promote polarization of CD4+ cells into TH2 cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, stimulate immune cells, modulate immune cell polarization, and/or mediate humoral or cell-mediated immunity.</p> <p>Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-4, and the stimulation of immune cells, such as B cells, T cells, macrophages and mast cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach"</p>	<p>Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-4 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-4 production. A highly preferred indication includes asthma. A highly preferred indication includes allergy. A highly preferred indication includes rhinitis. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications</p>
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				<p>Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):277-283 (1994); Yssel et al., Res Immunol 144(8):610-616 (1993); Bagley et al., Nat Immunol 1(3):257-261 (2000); and van der Graaff et al., Rheumatology (Oxford) 38(3):214-220 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
54	HDPND46	458	<p>Production of IL-8 by endothelial cells (such as Human Umbilical Cord Endothelial Cells).</p>	<p>Assays measuring production of IL-8 are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8. For</p>	<p>Highly preferred indications include immunological and inflammatory disorders (e.g., such as allergy, asthma, leukemia, etc. and as described below under "Immune Activity", and "Blood-Related Disorders"). Highly preferred indications also include autoimmune</p>

				<p>example, FMAT may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8 from endothelial cells (such as human umbilical vein endothelial cells (HUVEC)). HUVECs are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Endothelial cells play a pivotal role in the initiation and perpetuation of inflammation and secretion of IL-8 may play an important role in recruitment and activation of immune cells such as neutrophils, macrophages, and lymphocytes.</p>	<p>disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), neoplastic disorders (e.g., organ cancers such as lung, liver, colon cancer, and/or as described below under "Hyperproliferative Disorders"), and cardiovascular disorders (e.g. such as described below under "Cardiovascular Disorders"). Preferred indications include thrombosis, bacteremia and sepsis syndrome and consequent complications (such as acute respiratory distress syndrome and systemic ischemia-reperfusion resulting from septic shock), restenosis and atherosclerosis.</p>
55	HDPO108	459	<p>Inhibition of squalene synthetase gene transcription.</p>	<p>Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824 (1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science.</p>	

55	HDPOJ08	459	Regulation of apoptosis in pancreatic beta cells.	<p>209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.</p> <p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially</p>
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56	HDPN86	460	are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
			Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma,

			<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
57	HDPSB18	461	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as</p>

			secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.	described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
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58	HDPSH53	462	Stimulation of Calcium Flux in pancreatic beta cells.	<p>References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal</p>
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				publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
58	HDP5H53	462	Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used</p>	

59	HDPSP01	463	Production of MCP-1	<p>or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4: 193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an</p>
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				<p>agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T</p>	<p>infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include</p>
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59	HDPSP01	463	Insulin Secretion	<p>cell proliferation and functional activities.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K.,</p>	<p>neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>
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				<p>et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
60	HDPSP54	464	Activation of Endothelial Cell JNK Signaling Pathway.	<p>Kinase assay. JNK kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly</p>

				<p>JNK kinase activity that may be used or routinely modified to test JNK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention include a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart</p>
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					<p>disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders").</p> <p>Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma,</p>
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					<p>angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft</p>
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					<p>rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p>
60	HDPSP54	464	<p>Regulation of apoptosis in pancreatic beta cells.</p>	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy</p>

				<p>promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krauthelm, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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				line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.	associated with insulin resistance.
60	HDPSP54	464	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these	Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.

				assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.	
61	HDPUH26	465	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM,	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred

				<p>Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>
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					<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery</p>
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					disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
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62	Adipocyte ERK Signaling Pathway	<p>example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell</p>	<p>of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or</p>
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				<p>line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>"Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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					<p>and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign</p>
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62	HDPUIW68	466	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2	dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.  A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative
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				dependent suspension culture of T cells with cytotoxic activity.	Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
62	HDPW68	466	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with

			<p>invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., <i>Endocrinology</i>, 136(10):4589-601 (1995); Mogami H, et al., <i>Endocrinology</i>, 136(7):2960-6 (1995); Richardson SB, et al., <i>Biochem J</i>, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., <i>Cell Calcium</i> 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial</p>	<p>diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or</p>
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				cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
62	HDPW68	466	Activation of Skeletal Muscle Cell PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein</p> <p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred</p>	

				<p>incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood</p>
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					<p>vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy,</p>
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				<p>and/or as described herein.</p> <p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, and arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysplastic disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p>
63	HDPWU34	467	<p>Activation of Adipocyte P13 Kinase Signalling Pathway</p>	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for P13 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for P13 kinase activity that may be used or routinely modified to test P13 kinase-induced activity of polypeptides of the</p> <p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for</p>

			<p>invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy,</p>
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					<p>nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the</p>
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					<p>musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders.</p> <p>Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer.</p> <p>Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
63	HDPWU34	467	<p>Activation of transcription through GAS response element in immune cells (such as eosinophils).</p>	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate gene expression (commonly via STAT transcription factors) involved in a wide variety of cell functions. Exemplary assays for</p>	<p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below),</p>

				<p>transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995); the contents of each of which are herein incorporated by reference in its entirety. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate or inhibit activation of immune cells include assays disclosed and/or cited in: Mayumi M., "EoL-1, a human eosinophilic cell line" Leuk Lymphoma; Jun;7(3):243-50 (1992); Bhattacharya S, "Granulocyte macrophage colony-stimulating factor and interleukin-5 activate STAT5 and induce CIS1 mRNA in human peripheral blood eosinophils" Am J Respir Cell Mol Biol; Mar;24(3):312-6 (2001); and, Du J,</p>	<p>immunodeficiencies (e.g., as described below), boosting an eosinophil-mediated immune response and, alternatively, suppressing an eosinophil-mediated immune response.</p>
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				<p>et al., "Engagement of the CrkL adapter in interleukin-5 signaling in eosinophils" J Biol Chem; Oct 20;275(42):33167-75 (2000); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are a type of immune cell important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Increases in GAS mediated transcription in eosinophils is typically a result of STAT activation, normally a direct consequence of interleukin or other cytokine receptor stimulation (e.g. IL3, IL5 or GMCSF).</p> <p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo6 Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the</p>	
63	HDPWU34	467	Proliferation of pre-adipose cells (such as 3T3-L1 cells)		

				<p>presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.</p>	
63	HDPWU34	467	Activation of Transcription	<p>Assays for activation of transcription are well-known in the art and may be used and routinely modified to assess ability of polypeptides of the invention to inhibit or activate transcription. An example of such an assay follows: Cells were pretreated with SID supernatants or controls for 15-18 hours. SEAP activity was measured after 48 hours. LS174T is an epithelial colon adenocarcinoma cell line. Its tumorigenicity in nude mice make cell line LS174T a model for studies on the mechanism of synthesis and secretion of specific tumoral markers in colon cancer. See, Patan et al., Circ Res, 89(8):732-39 (2001), the contents of which are herein incorporated by reference in its entirety.</p>	
64	HDPXY01	468	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy,</p>	



			<p>and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet</p>	<p>diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional</p>
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				cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	highly preferred indications are complications associated with insulin resistance.
65	HDTBV77	469	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of	A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the

				<p>the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
66	HDTDQ23	470	Endothelial Cell Apoptosis	Caspase Apoptosis. Assays for caspase apoptosis are well known in	A highly preferred embodiment of the invention includes a method for

				<p>the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Induction of apoptosis in endothelial cells supporting the vasculature of tumors is associated with tumor regression due to loss of tumor blood supply. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell</p>	<p>stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative</p>
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				extravasation.	<p>Disorders”), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under “Cardiovascular Disorders”). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi’s sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi’s sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary</p>
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					<p>angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis.</p>
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66	HDTDQ23	470	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and	Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment/prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
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			<p>agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT T15 Cells. HIT T15 are an adherent epithelial cell line established from Syrian</p>	<p>diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyposmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p>
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67	HE2DE47	471	Regulation of apoptosis in pancreatic beta cells.	<p>hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et</p>	<p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>
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				<p>al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
68	HE2NV57	472	Activation of T-Cell p38 or JNK Signaling Pathway.	<p>Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g.</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly</p>

			<p>T-cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9): 1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.</p>	<p>preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p>
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68	HE2NV57	472	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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				<p>Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
69	HE2PH36	473	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension,</p>

				<p>antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17711-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
	HE8DS15	474	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention</p>	

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				<p>ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a</p>
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					<p>complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight</p>
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					<p>gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
70	HE8DS15	474	Regulation of Malic transcription of Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy</p>

				<p>invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeter, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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70	HE8DS15	474	Inhibition of squalene synthetase gene transcription.	assays includes the H4IIE rat liver hepatoma cell line. Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824 (1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	associated with insulin resistance.
71	HE9CO69	475	Production of IL-8 by endothelial cells (such as Human Umbilical Cord Endothelial Cells).	Assays measuring production of IL-8 are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8. For example, FMAT may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8 from endothelial cells (such as human umbilical vein endothelial cells (HUVEC)). HUVECs are	Highly preferred indications include immunological and inflammatory disorders (e.g., such as allergy, asthma, leukemia, etc. and as described below under "Immune Activity", and "Blood-Related Disorders"). Highly preferred indications also include autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), neoplastic disorders (e.g., organ cancers such as lung, liver, colon cancer, and/or as described below under "Hyperproliferative Disorders"), and cardiovascular disorders (e.g. such as described

72	HE9HY07	476	<p>endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Endothelial cells play a pivotal role in the initiation and perpetuation of inflammation and secretion of IL-8 may play an important role in recruitment and activation of immune cells such as neutrophils, macrophages, and lymphocytes.</p>	<p>below under "Cardiovascular Disorders"). Preferred indications include thrombosis, bacteremia and sepsis syndrome and consequent complications (such as acute respiratory distress syndrome and systemic ischemia-reperfusion resulting from septic shock), restenosis and atherosclerosis.</p>
			<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999);</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine</p>

				<p>disorders (e.g., as described below under "Endocrine Disorders").</p> <p>Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel</p>
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Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.

					<p>blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones,</p>
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					<p>osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
72	HE9HY07	476	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart</p>

				<p>or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
73	HE9OW20	477	<p>Activation of Skeletal Muscle Cell ERK Signalling Pathway</p>	<p>Kinase assay. Kinase assays, for examplek Elk-1 kinase assays, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and</p>	<p>Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders") and disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular</p>



				<p>differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision</p>
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					<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p> <p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Highly preferred indications also include breast, lung, colon, pancreatic, brain, and liver</p>
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74	HEEAG23	478	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these</p>	<p>cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood</p>
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				<p>assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>
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					<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include</p>
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74	HEEAG23	478	Activation of Skeletal Muscle Cell PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may</p>	<p>melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting</p>
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				<p>be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>
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					<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred</p>
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					indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.
					A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma,

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
76	HEPAB80	480	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of</p>

			agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below
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					<p>under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication</p>
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					is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternately, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
76	HEPAB80	480	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a

				<p>used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., <i>Endocrinology</i>, 139(1):172-8 (1998); Krautheim A, et al, <i>Exp Clin Endocrinol Diabetes</i>, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin,</p>	<p>complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred</p>
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77	HFABG18	481	Activation of Adipocyte ERK Signaling Pathway	<p>and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of</p>	<p>indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
				<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g.,</p>	

				<p>each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart</p>
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					<p>disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include</p>
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				<p>entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders").</p>
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					<p>Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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					<p>and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vasculitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred</p>
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					indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
					<p>IFNgamma FMAT. IFNγ plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNγ promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the</p>
					<p>A highly preferred embodiment of the invention includes a method for stimulating the production of IFNγ. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNγ. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune</p>
77	HFABG18	481	Production of IFNgamma using a T cells		

			<p>invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8.</p>	<p>disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory</p>
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78	HFABH95	482	Stimulation of insulin secretion from pancreatic beta cells.	<p>These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated</p>	<p>bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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				<p>by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
79	HFAEF57	483	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>

				<p>promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
	HFCEB37	484	<p>Regulation of Malic Enzyme in adipocytes</p>	<p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p>	

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				<p>ME promoter contains two direct repeat (DR1)-like elements. MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
81	HFFAD59	485	Regulation of transcription via DMEF1 response	Assays for the regulation of transcription through the DMEF1 response element are well-known in	A highly preferred indication is diabetes mellitus. Additional highly preferred indications include

			<p>element in adipocytes and pre-adipocytes</p>	<p>the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et</p>	<p>complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight</p>
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				<p>al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
81	HFFAD59	485	<p>Activation of transcription through API response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the API response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention (including antibodies and agonists or</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as</p>

				<p>antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.</p>	<p>described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p>
81	HFFAD59	485	<p>Activation of transcription through serum response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating</p>

			<p>invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>(e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign</p>
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					<p>dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
82	HFGAD82	486	<p>Activation of transcription through API response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the API response element are known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis</p>



				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the HT2 cell line, which is an IL-2 dependent suspension culture cell line that also responds to IL-4.</p>	<p>and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p>
82	HFGAD82	486	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with</p>

			<p>the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable</p>	<p>diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or</p>
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84	HFIUR10	488	Regulation of viability and proliferation of pancreatic beta cells.	<p>insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107(1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g.,</p>	<p>alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g.,</p>
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				through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
85	HFKFG02	489	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al.,	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the

				<p>Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karn, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity"; "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy,</p>
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					<p>nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular</p>
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					<p>dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
86	HFTBM50	490	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>

				<p>diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATCC# CRL-1777</p> <p>Refs: Lord and Ashcroft. <i>Biochem. J.</i> 219: 547-551; Santerre et al. <i>Proc.</i></p>	<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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86	HFTBM50	490	Production of IL-10 and activation of T-cells.	<p>Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology &amp; Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2</p>	<p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.</p>
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87	HFTDZ36	491	Protection from Endothelial Cell Apoptosis.	<p>cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.</p> <p>Caspase Apoptosis Rescue. Assays for caspase apoptosis rescue are well known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to inhibit caspase protease-mediated apoptosis. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis rescue of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Romeo et al., Cardiovasc Res 45(3): 788-794 (2000); Messmer et al., Br J Pharmacol 127(7): 1633-1640 (1999); and J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred</p>
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				<p>(bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or</p>
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					<p>lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's</p>
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					phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vasculitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus
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					erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.
87	HFTDZ36	491	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett. 377(2):237-9	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the

				<p>(1995); and, Miraglia S et. al., Journal of Biomolecular Screenings, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
88	HEXBL33	492	<p>Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes</p>	<p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental</p>

				<p>transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEFI response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an</p>	<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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89	HFXHK73	493	Activation of Adipocyte ERK Signaling Pathway	adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as
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				<p>incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>
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					<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as,</p>
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					lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
90	HFXJX44	494	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology,	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section

				<p>138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
91	HEXKY27	495	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A</p>

				<p>kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy,</p>
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					<p>diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are</p>
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91	HFXKY27	495	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to	Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's
					<p>complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>



				<p>regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.</p>	<p>lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia,</p>
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92	HGBHI35	496	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824 (1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
92	HGBHI35	496	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy

				<p>secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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93	HGLAF75	497	Regulation of transcription of Malic Enzyme in hepatocytes	<p>glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements. MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988);</p>	<p>associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially</p>
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				and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
93	HGLAF75	497	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma,

				<p>proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
93	HGLAF75	497	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>

			<p>using anti-rat insulin antibodies.</p> <p>Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is</p>	<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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94	HHBCS39	498	Activation of Adipocyte ERK Signaling Pathway	<p>stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under</p>
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				<p>entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>“Hyperproliferative Disorders”). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under “Immune Activity”, “Cardiovascular Disorders”, and/or “Blood-Related Disorders”), immune disorders (e.g., as described below under “Immune Activity”), neural disorders (e.g., as described below under “Neural Activity and Neurological Diseases”), and infection (e.g., as described below under “Infectious Disease”).</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the “Renal Disorders” section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension,</p>
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					stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast,
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					colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
94	HHBCS39	498	TNF $\alpha$ in Human T-cell 2B9		
95	HHEAA08	499	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM,</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred</p>

				<p>Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is 'diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>
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					<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery</p>
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					<p>disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
95	HHEAA08	499	CD152 in Human T cells		
95	HHEAA08	499	RANTES in Human T cells		
95	HHEAA08	499	IL-5 in Th2		
97	HHFFJ48	501	Activation of Adipocyte PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival.</p>	<p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention</p>

				<p>Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease</p>
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					<p>(e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred</p>
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					<p>indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
98	HHFHJ59	502	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation	<p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus,</p>

				<p>of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology &amp; Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.</p>	<p>Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.</p>
99	HHGBO91	503	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly</p>

			<p>are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo</p>	<p>preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural</p>
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					<p>a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as</p>
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					<p>described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternately, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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100	HHGCG53	504	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may</p>	<p>and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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				<p>be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
101	HHGCM76	505	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>

				<p>(1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
101	HHGCM76	505	Production of ICAM-1	<p>Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Inflammation, Vascular Disease, Atherosclerosis, Restenosis, and Stroke</p>



102	HHGCQ54	506	Activation of Adipocyte ERK Signaling Pathway	<p>incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g.,</p>
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				<p>each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart</p>
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					<p>disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include</p>
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103	HHPEN62	507	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include	neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
				<p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>	

103	HHPEN62	507	Proliferation of pre-adipose cells (such as 3T3-L1 cells)	<p>assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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				agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo <sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.	
103	HHPEN62	507	Activation or inhibition of transcription through NFKB response element in immune cells (such as basophils).	This reporter assay measures activation or inhibition of the NFKB signaling pathway in Ku812 human basophil cell line. Assays for the activation or inhibition of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. NFKB is	

				<p>important in the pathogenesis of asthma. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Cells were pretreated with SID supernatants or controls for 15-18 hours, and then 10 ng/mL of TNF was added to stimulate the NFkB reporter. SEAP activity was measured after 48 hours. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils. See, Kishi et al., Leuk Res. 9:381-390 (1985); Blom et al., Eur J Immunol. 22:2025-32</p>	
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104	HJABB94	508	Inhibition of squalene synthetase gene transcription.	<p>(1992), where the contents of each are herein incorporated by reference in its entirety.</p> <p>Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824 (1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.</p>	
104	HJABB94	508	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic</p>	



				<p>(from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
HJACG02	509	Proliferation of pre-	Assays for the regulation (i.e.		

105			adipose cells (such as 3T3-L1 cells)	<p>increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo<sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.</p>	
106	HJACG30	510	Activation of transcription through serum response element in immune cells (such as T-cells).	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum</p> <p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as</p>	

				<p>response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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					and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
106	HJACG30	510	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	

106	HJACG30	510	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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107	HJBCY35	511	Regulation of viability and proliferation of pancreatic beta cells.	<p>include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem</p>	<p>highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
				<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>	

			<p>1998 Jul 10;273(28):1771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
107	HJBCY35	511	<p>Activation of Skeletal Muscle Cell PI3 Kinase Signalling Pathway</p>	<p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A</p>

				<p>invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic</p>
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					<p>nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p>
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108	HJPAD75	512	Activation of T-Cell p38 or JNK Signaling Pathway.	Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to	Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.
					Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below

				<p>promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.</p>	<p>under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis,</p>
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108	HIPAD75	512	Production of IL-6	<p>IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention</p>	<p>meningitis, and Lyme Disease.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as</p>
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				<p>(including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
108	HIPAD75	512	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease</p>

				<p>(including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 ( Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible</p>	<p>(e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred</p>
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108	HJPAD75	512	Proliferation of pre-adipose cells (such as 3T3-L1 cells)	with glucocorticoids, insulin, or cAMP derivatives. Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo <sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.	indications are complications associated with insulin resistance.
108	HJPAD75	512	IFNg in Human T-cell 2B9		
109	HKABZ65	513	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly

				<p>IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al.,</p>	<p>preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia,</p>
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				<p>"Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
109	HKABZ65	513	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	<p>Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly</p>

				<p>assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) the activation of and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative</p>
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					Disorders”), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under “Cardiovascular Disorders”). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi’s sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi’s sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary
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					<p>angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis.</p>
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109	HKABZ65	513	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention	<p>Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy,</p>
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				<p>(including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krauthaim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include</p>	<p>diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p>
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				<p>RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>Additional highly preferred indications are complications associated with insulin resistance.</p>
110	HKACD58	514	<p>Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes</p>	<p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>

				<p>the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
110	HKACD58	514	Activation of transcription through	Assays for the activation of transcription through the Serum	A preferred embodiment of the invention includes a method for



			<p>serum response element in immune cells (such as natural killer cells).</p>	<p>Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate,</p>
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					breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
111	HKAEV06	515	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy,

				<p>luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krautheim A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc.</p>	<p>nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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				Natl. Acad. Sci. USA 78: 4339-4343, 1981.	
111	HKAEV06	515	Activation of Transcription	Assays for activation of transcription are well-known in the art and may be used and routinely modified to assess ability of polypeptides of the invention to inhibit or activate transcription. An example of such an assay follows: Cells were pretreated with SID supernatants or controls for 15-18 hours. SEAP activity was measured after 48 hours. LS174T is an epithelial colon adenocarcinoma cell line. Its tumorigenicity in nude mice make cell line LS174T a model for studies on the mechanism of synthesis and secretion of specific tumoral markers in colon cancer. See, Patan et al., Circ Res, 89(8):732-39 (2001), the contents of which are herein incorporated by reference in its entirety.	
111	HKAEV06	515	Activation of transcription through API response element in immune cells (such as T-cells).	Assays for the activation of transcription through the API response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention	Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and

				<p>(including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.</p>	<p>immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p>
112	HKAFT66	516	Myoblast cell proliferation	<p>Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and</p>	<p>Highly preferred indications include diabetes, myopathy, muscle cell atrophy, cancers of muscle (such as, rhabdomyoma, and rhabdosarcoma), cardiovascular disorders (such as</p>

				<p>agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al., "Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, vascular disease, and also as described below under "Cardiovascular Disorders"), stimulating myoblast proliferation, and inhibiting myoblast proliferation.</p>
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112	HKAF66	516	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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				<p>Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
112	HKAFT66	516	<p>Activation of transcription through GATA-3 response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma,</p>



				<p>response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
112	HKAFT66	516	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and</p>

			<p>the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly</p>	<p>inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted</p>
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113	HKBIE57	517	Regulation of viability and proliferation of pancreatic beta cells.	<p>available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem</p>	<p>organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>
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				<p>1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
113	HKBIES7	517	<p>Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>RANTES FMAAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune</p>	

114	HKFBC53	518	Regulation of transcription of Malic Enzyme in adipocytes	<p>cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as</p>
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				<p>Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements. MEp and MEd identified as putative PPAR response elements. ME promoter may also respond to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver</p>	<p>described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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115	HKGDL36	519	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>hepatoma cell line.</p> <p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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				these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
115	HKGDL36	519	Proliferation of pre-adipose cells (such as 3T3-L1 cells)	Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo <sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein	



115	HKGDL36	519	Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>incorporated by reference in its entirety.</p> <p>RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may</p>	
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115	HKGDL36	519	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FRET may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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116	HKISB57	520	<p>Activation of JNK Signaling Pathway in immune cells (such as eosinophils).</p>	<p>cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p> <p>Kinase assay. JNK kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK kinase activity that may be used or routinely modified to test JNK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays</p>	<p>and/or dysplasia.</p> <p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting or inhibiting immune cell proliferation. Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include boosting an eosinophil-mediated immune response, and suppressing an eosinophil-mediated immune response.</p>
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				<p>include eosinophils. Eosinophils are important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate signal transduction, cell proliferation, activation, or apoptosis in eosinophils include assays disclosed and/or cited in: Zhang JP, et al., "Role of caspases in dexamethasone-induced apoptosis and activation of c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in human eosinophils" Clin Exp Immunol; Oct;122(1):20-7 (2000); Hebestreit H, et al., "Disruption of fas receptor signaling by nitric oxide in eosinophils" J Exp Med; Feb 2;187(3):415-25 (1998); J Allergy Clin Immunol 1999 Sep;104(3 Pt 1):565-74; and, Sousa AR, et al., "In vivo resistance to corticosteroids in bronchial asthma is associated with enhanced phosphorylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation" J Allergy Clin Immunol; Sep;104(3 Pt 1):565-74 (1999); the contents of each of which are herein incorporated by reference</p>	
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116	HKISB57	520	Regulation of transcription of Malic Enzyme in adipocytes	<p>in its entirety.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DRI)-like elements MEp and ME<sub>d</sub> identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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				<p>contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.</p>	<p>contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
117	HKMMW74	521	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>

				<p>1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
118	HLDNA86	522	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative</p>

				<p>the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>
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					<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems</p>
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					including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
119	HLDON23	523	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>

			<p>may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p>
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					<p>Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-</p>
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119	HLDON23	523	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.	neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
119	HLDON23	523	Production of ICAM-1	Assays for measuring expression of ICAM-1 are well-known in the art	Preferred embodiments of the invention include using polypeptides

				<p>and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).</p>	<p>of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Inflammation, Vascular Disease, Atherosclerosis, Restenosis, and Stroke</p>
119	HLDON23	523	<p>Production of IL-10 and activation of T-cells.</p>	<p>Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the</p>	<p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and</p>

				<p>invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology &amp; Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.</p>	<p>suppressing a T cell-mediated immune response.</p>
120	HLDQR62	524	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>

			<p>For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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120	HLDQR62	524	<p>Activation of transcription through cAMP response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2</p>	<p>Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example,</p>
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121	HLDQU79	525		dependent cytotoxic T cells.	hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.
				Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and

				<p>assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
121	HLDQU79	525	<p>Activation of transcription through serum response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred</p>

				<p>may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's</p>
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					<p>disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
122	HLHAL68	526	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension,</p>

				antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
123	HLIBD68	527	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described

				<p>differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these</p>	<p>below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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				assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
123	HLIBD68	527	Production of MIP1alpha	MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation	A highly preferred embodiment of the invention includes a method for stimulating MIP 1a production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MIP 1a production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus,



				<p>of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>	<p>A highly preferred embodiment of</p>
HLIBD68	527	Production of TNF	TNFα FMAT. Assays for			

123			alpha by dendritic cells	<p>immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNF<math>\alpha</math>), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1998); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828</p>	<p>the invention includes a method for inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma),</p>
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				<p>(1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
123	HLIBD68	527	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>

			<p>using anti-rat insulin antibodies.</p> <p>Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4: 193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al.</p>	<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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124	HLICQ90	528	<p>Activation of transcription through serum response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for</p>
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124	HLICQ90	528	Production of TNF alpha by dendritic cells	TNFα FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells	<p>example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF</p>
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			<p>are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFα), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1998); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or</p>	<p>alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysplastic disorders and pre-neoplastic</p>
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				<p>otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
124	HLICQ90	528	<p>Stimulation of Calcium Flux in pancreatic beta cells.</p>	<p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel</p>



				<p>calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci.</p>	<p>blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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124	HLICQ90	528	Stimulation of insulin secretion from pancreatic beta cells.	<p>USA 78: 4339-4343, 1981.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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				<p>be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Aditional highly preferred indications are complications associated with insulin resistance.</p>
125	HLQDR48	529	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders").</p>

				<p>MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic</p>
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					<p>hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia,</p>
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125	HLQDR48	529	Production of MCP-I	<p>MCP-I FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely</p>	<p>and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-I production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-I production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis,</p>
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				<p>modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
125	HLQDR48	529	Production of TNF alpha by dendritic cells	TNFα FMAT. Assays for immunomodulatory proteins	<p>A highly preferred embodiment of the invention includes a method for</p>

				<p>produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFα), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1998); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which</p>	<p>inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast,</p>
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				are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.	lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
126	HLTHR66	530	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies.	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy,

				<p>Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. <i>Endocrinology</i> 1992 130:167.</p>	<p>nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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127	HLTIP94	531	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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128	HLWAA17	532	Regulation of Malic transcription of Malic Enzyme in adipocytes	<p>include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)- like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also respond to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998);</p>	<p>highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
				<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>	

				<p>Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.</p>	<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
128	HLWAA17	532	Production of ICAM-1	<p>Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Inflammation, Vascular Disease, Atherosclerosis, Restenosis, and Stroke</p>

				according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).	
129	HLWBK05	533	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under</p>

				<p>entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>“Hyperproliferative Disorders”). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under “Immune Activity”, “Cardiovascular Disorders”, and/or “Blood-Related Disorders”), immune disorders (e.g., as described below under “Immune Activity”), neural disorders (e.g., as described below under “Neural Activity and Neurological Diseases”), and infection (e.g., as described below under “Infectious Disease”). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the “Renal Disorders” section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension,</p>
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					stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast,
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130	HLWBY76	534	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of		colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
				A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory		

				<p>which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and</p>
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131	HLWCF05	535	Activation of Adipocyte PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an</p>	<p>allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below</p>
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				<p>adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>
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					<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p> <p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders.</p> <p>Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung,</p>
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131	HLWCF05	535	Activation of JNK Signaling Pathway in immune cells (such as eosinophils).	<p>Kinase assay. JNK kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK kinase activity that may be used or routinely modified to test JNK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays</p>	<p>pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting or inhibiting immune cell proliferation. Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include boosting an eosinophil-mediated immune response, and suppressing an eosinophil-mediated immune response.</p>
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				<p>include eosinophils. Eosinophils are important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate signal transduction, cell proliferation, activation, or apoptosis in eosinophils include assays disclosed and/or cited in: Zhang JP, et al., "Role of caspases in dexamethasone-induced apoptosis and activation of c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in human eosinophils" Clin Exp Immunol; Oct;122(1):20-7 (2000); Hebestreit H, et al., "Disruption of fas receptor signaling by nitric oxide in eosinophils" J Exp Med; Feb 2;187(3):415-25 (1998); J Allergy Clin Immunol 1999 Sep;104(3 Pt 1):565-74; and, Sousa AR, et al., "In vivo resistance to corticosteroids in bronchial asthma is associated with enhanced phosphorylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation" J Allergy Clin Immunol; Sep;104(3 Pt 1):565-74 (1999); the contents of each of which are herein incorporated by reference</p>
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131	HLWCF05	535	<p>Activation of transcription through API response element in immune cells (such as T-cells).</p>	<p>in its entirety.</p> <p>Assays for the activation of transcription through the API response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma,</p>
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131	HLWCF05	535	<p>Activation of transcription through CD28 response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol</p>	<p>IL-4 responsive suspension-culture cell line.</p>	<p>AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune</p>
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				<p>Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p> <p>diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Highly preferred indications include neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma (e.g., metastatic melanoma), renal cell carcinoma (e.g., metastatic renal cell carcinoma), leukemia, lymphoma (e.g., T cell lymphoma), and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. A highly preferred indication includes infection (e.g., AIDS, tuberculosis, infections associated with granulomatous disease, and osteoporosis, and/or as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred</p>
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					<p>indications include suppression of immune reactions to transplanted organs and/or tissues, uveitis, psoriasis, and tropical spastic paraparesis. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
131	HLWCF05	535	<p>Activation of transcription through NFAT response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or</p>	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly</p>

				<p>routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
	HLWCF05	535	Activation of	Assays for the activation of	Highly preferred indications

131	transcription through NFKB response element in immune cells (such as T-cells).	transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.	include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia,
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					thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.
132	HLYAC95	536	Production of IFNgamma using a T cells	IFNgamma FMAT. IFNγ plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNγ promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated	A highly preferred embodiment of the invention includes a method for stimulating the production of IFNγ. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNγ. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-

				<p>immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus,</p>
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132	HLYAC95	536	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated.</p>	<p>endocarditis, meningitis, Lyme Disease, asthma and allergy.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal</p>
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				<p>Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
133	HLVAN59	537	<p>Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-I expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>

				cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.	and/or dysplasia.
134	HLYP91	538	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under</p>

				<p>entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>“Hyperproliferative Disorders”). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under “Immune Activity”, “Cardiovascular Disorders”, and/or “Blood-Related Disorders”), immune disorders (e.g., as described below under “Immune Activity”), neural disorders (e.g., as described below under “Neural Activity and Neurological Diseases”), and infection (e.g., as described below under “Infectious Disease”). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the “Renal Disorders” section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension,</p>
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					stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast,
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135	HLYES38	539	Activation of Adipocyte PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein</p>	<p>colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications</p>
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				<p>incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart</p>
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					<p>disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia,</p>
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136	HMADK33	540	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992);	<p>and kidney diseases or disorders. Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and</p>
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				<p>Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988);  Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas.</p>
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					Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"). Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
137	HMADS41	541	Protection from Endothelial Cell Apoptosis.	Caspase Apoptosis Rescue. Assays for caspase apoptosis rescue are well known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and	A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting

				<p>agonists or antagonists of the invention) to inhibit caspase protease-mediated apoptosis. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis rescue of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Romeo et al., Cardiovasc Res 45(3): 788-794 (2000); Messmer et al., Br J Pharmacol 127(7): 1633-1640 (1999); and J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly</p>
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					<p>preferred indications include neoplastic diseases (e.g., as described below under “Hyperproliferative Disorders”), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under “Cardiovascular Disorders”).</p> <p>Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi’s sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as,</p>
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					<p>Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury,</p>
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					<p>rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p>
137	HMADS41	541	Activation of Hepatocyte ERK	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for	A highly preferred embodiment of the invention includes a method for

		Signaling Pathway	<p>ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat liver hepatoma cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat liver hepatoma cells that may be used according to these assays include H4IIE cells, which are known to respond to glucocorticoids, insulin, or cAMP derivatives.</p>	<p>stimulating hepatocyte cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell differentiation. A highly preferred embodiment of the invention includes a method for activating hepatocyte cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating hepatocyte cells. Highly preferred indications include disorders of the liver and/or endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and</p>
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					<p>infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal</p>
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					<p>tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p> <p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include, hepatitis, jaundice, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism.</p> <p>Additional highly preferred indications include neoplasms and cancers, such as, hepatocarcinomas, other liver cancers, and colon and pancreatic cancer. Preferred indications also include prostate, breast, lung, esophageal, stomach, brain, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
					<p>Regulation of apoptosis</p>
					<p>Caspase Apoptosis. Assays for</p>
					<p>541</p>
					<p>HMADS41</p>
					<p>Preferred embodiments of the</p>

137			<p>of immune cells (such as mast cells).</p>	<p>caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate caspase protease-mediated apoptosis in immune cells (such as, for example, in mast cells). Mast cells are found in connective and mucosal tissues throughout the body, and their activation via immunoglobulin E -antigen, promoted by T helper cell type 2 cytokines, is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity induced by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Masuda A, et al., J Biol Chem, 276(28):26107-26113 (2001); Yeatman CF 2nd, et al., J Exp Med, 192(8):1093-1103 (2000); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be</p>	<p>invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of asthma, allergy, hypersensitivity and inflammation.</p>
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138	HMAMI15	542	Stimulation of Calcium Flux in pancreatic beta cells.	<p>used according to these assays are publicly available (e.g., through commercial sources). Exemplary immune cells that may be used according to these assays include mast cells such as the HMC human mast cell line.</p> <p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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138	HMAM115	542	Activation of Transcription	<p>Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for activation of transcription are well-known in the art and may be used and routinely modified to assess ability of polypeptides of the invention to inhibit or activate transcription. An example of such an assay follows: Cells were pretreated with SID supernatants or controls for 15-18 hours. SEAP activity was measured after 48 hours. LS174T is an epithelial colon adenocarcinoma cell line. Its tumorigenicity in nude mice make cell line LS174T a model for studies on the mechanism of</p>	<p>wound healing, and infection (e.g., in infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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139	HMC FY13	543	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	<p>synthesis and secretion of specific tumoral markers in colon cancer. See, Patan et al., Circ Res, 89(8):732-39 (2001), the contents of which are herein incorporated by reference in its entirety.</p> <p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S.,</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g.,</p>
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				et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
				Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy
140	HMDAB56	544	Regulation of transcription through the PEPCK promoter in hepatocytes		

				<p>antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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					<p>associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas.</p> <p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate,</p>
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141	HMEED18	545	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al.,	breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
				A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision	

				<p>Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
141	HMEED18	545	<p>Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral</p>	



				<p>the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be</p>	<p>additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with</p>
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					<p>routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057</p> <p>Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
143	HMEGF92	547	Production of ICAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>Endothelial cells, which are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Exemplary endothelial cells that may be used in ICAM production assays include human umbilical vein endothelial cells (HUVEC), and are available from commercial sources. The expression of ICAM (CD54), a integral membrane protein, can be upregulated by cytokines or other factors, and ICAM expression is important in mediating immune and endothelial cell interactions leading to immune and inflammatory responses. Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-</p>	

				<p>invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., <i>Atherosclerosis</i>, 149(1):99-110 (2000); Panettieri RA Jr, et al., <i>J Immunol</i>, 154(5):2358-2365 (1995); and, Grunstein MM, et al., <i>Am J Physiol Lung Cell Mol Physiol</i>, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety.</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
143	HMEGF92	547	<p>Regulation of apoptosis in pancreatic beta cells.</p>	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., <i>FEBS Lett</i>, 400(3):285-8 (1997); Saini, KS, et al., <i>Biochem Mol Biol Int</i>, 39(6):1229-36 (1996);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension,</p>

				<p>Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057</p> <p>Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
144	HMSDL37	548	Regulation of viability and proliferation of pancreatic beta cells.	Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy,

				<p>invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplatable insulinoma. These cells retain characteristics typical of</p>	<p>diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional</p>
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145	HMSF126	549	Stimulation of insulin secretion from pancreatic beta cells.	<p>native pancreatic beta cells including glucose inducible insulin secretion. References: Afari et al. Endocrinology 1992 130:167.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly</p>	<p>highly preferred indications are complications associated with insulin resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious</p>
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146	HMSJU68	550	Activation of transcription through NFKB response element in immune cells (such as EOL1 cells).	<p>available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci</p>	<p>Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, and inflammation. Preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), immunological disorders, inflammation and inflammatory disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).</p>
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146	HMSJU68	550	Regulation of apoptosis of immune cells (such as mast cells).	<p>USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFkB element to a reporter gene and binds to the NFkB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils.</p> <p>Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of asthma, allergy, hypersensitivity and inflammation.</p>
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				<p>cells are found in connective and mucosal tissues throughout the body, and their activation via immunoglobulin E -antigen, promoted by T helper cell type 2 cytokines, is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity induced by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Masuda A, et al., J Biol Chem, 276(28):26107-26113 (2001); Yeatman CF 2nd, et al., J Exp Med, 192(8):1093-1103 (2000); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary immune cells that may be used according to these assays include mast cells such as the HMC human mast cell line.</p>	<p>A highly preferred embodiment of the invention includes a method for</p>
146	HMSJU68	550	Activation of Skeletal Muscle Cell PI3 Kinase	<p>Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for</p>	

			<p>PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as</p>
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					described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the
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					<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications</p>
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147	HMTBI36	551	Activation of transcription through NFKB response element in immune cells (such as EOL1 cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Arambour et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference	also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications include asthma, allergy, hypersensitivity reactions, and inflammation. Preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), immunological disorders, inflammation and inflammatory disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).
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				<p>in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFkB element to a reporter gene and binds to the NFkB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils.</p> <p>Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.</p>	
147	HMTBI36	551	Activation of Skeletal Muscle Cell PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and</p> <p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle</p>	

				<p>agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g.,</p>
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					<p>diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or</p>
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148	HMVBS81	552	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin	<p>alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer.</p> <p>Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p>
					<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as</p>

				<p>secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p>	<p>described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hypoglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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149	HMWDC28	553	Stimulation of insulin secretion from pancreatic beta cells.	<p>References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal</p>
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150	HMWFT65	554		<p>Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine</p>
				<p>Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and</p>	<p>tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>

				<p>pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
HNEEE24	555	Insulin Secretion	Assays for measuring secretion of	A highly preferred indication is	



151				<p>insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may</p>	<p>diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity</p>
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152	HNFFC43	556			<p>be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
				<p>Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and</p>	

			<p>that may be used or routinely modified to test for DMEFI response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion</p>	<p>disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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152	HNFFC43	556	Proliferation of immune cells (such as the HMC-1 human mast cell line)	<p>under appropriate differentiation culture conditions.</p> <p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of eosinophil cells and cell lines. For example, the CellTiter-Glo<sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA ) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Mast cells are found in connective and mucosal tissues throughout the body. Mast cell activation (via immunoglobulin E - antigen, promoted by T helper cell type 2 cytokines) is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Mast cell lines that may be used according to these assays are publicly available and/or may be routinely generated. Exemplary mast cells that may be used according to these assays include HMC-1, which is an immature human mast cell line</p>	<p>Highly preferred indications include asthma, allergy, mastocytosis (a rare, heterogeneous disorder characterized by excessive accumulation of mast cells, and their proliferation and action in the skin, central nervous system, and other organs). Preferred indications also include hematopoietic and immunological disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), infection (e.g., as described below under "Infectious Disease"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below).</p>
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152	HNFFC43	556	Activation of T-Cell p38 or JNK Signaling Pathway.	<p>established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for</p>
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152	HNF4C3	556	Regulation of transcription of Malic Enzyme in adipocytes	<p>used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and MEd identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and</p>	<p>example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>
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				agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
154	HNFIY77	558	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>	

				<p>diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. <i>Biochem. J</i>. 219: 547-551; Santerre et al. <i>Proc.</i></p>	<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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155	HNFJF07	559	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Natl. Acad. Sci. USA 78: 4339-4343, 1981. Assays for the regulation of response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair	A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An
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				<p>regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
155	HNF1F07	559	<p>Regulation of viability and proliferation of pancreatic beta cells.</p>	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage</p>

				<p>measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
155	HNF1F07	559	Activation of transcription through	Assays for the activation of transcription through the Serum	A preferred embodiment of the invention includes a method for

			<p>serum response element in immune cells (such as T-cells).</p>	<p>Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate,</p>
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155	HNF1F07	559	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies.	<p>breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy,</p>
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				<p>Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. <i>Endocrinology</i> 1992 130:167.</p>	<p>nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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156	HNGDJ72	560	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity",</p>
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				<p>adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>"Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision</p>
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				<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other</p>
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156	HNGDJ72	560	Production of IL-6	<p>IL-6 FMT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such</p>	<p>preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and</p>
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				<p>assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
156	HNGDJ72	560	Production of MIP1alpha	MIP-1alpha FMT. Assays for immunomodulatory proteins	<p>A highly preferred embodiment of the invention includes a method</p>

				<p>produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Erenin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by</p>	<p>for stimulating MIP1a production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MIP1a production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma, and allergy.</p>
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156	HNGDJ72	560		<p>reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
			Production of TNF alpha by dendritic cells	<p>TNFα FMA T. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFα), and the induction or inhibition of an inflammatory or cytotoxic response.</p>	<p>A highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and</p>

				<p>Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1998); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia,</p>
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156	HNGDJ72	560	Production of ICAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>Endothelial cells, which are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Exemplary endothelial cells that may be used in ICAM production assays include human umbilical vein endothelial cells (HUVEC), and are available from commercial sources. The expression of ICAM (CD54), a integral membrane protein, can be upregulated by cytokines or other factors, and ICAM expression is important in mediating immune and endothelial cell interactions leading to immune and inflammatory responses. Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include</p>	<p>hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>Highly preferred indications include inflammation (acute and chronic), restnosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
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156	HNGDJ72	560	Production of IL-8 by endothelial cells (such as Human Umbilical Cord Endothelial Cells).	assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety.	Highly preferred indications include immunological and inflammatory disorders (e.g., such as allergy, asthma, leukemia, etc. and as described below under "Immune Activity", and "Blood-Related Disorders"). Highly preferred indications also include autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), neoplastic disorders (e.g., organ cancers such as lung, liver, colon cancer, and/or as described below under "Hyperproliferative Disorders"), and cardiovascular disorders (e.g. such as described below under "Cardiovascular Disorders"). Preferred indications include thrombosis, bacteremia and sepsis syndrome and consequent complications (such as acute respiratory distress syndrome and systemic ischemia-reperfusion resulting from septic shock), restenosis and atherosclerosis.
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156	HNGDJ72	560	Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	may play an important role in recruitment and activation of immune cells such as neutrophils, macrophages, and lymphocytes. RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein	
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156	HNGDJ72	560	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-</p>
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157	HNGEP09	561	Activation of transcription through serum response element in immune cells (such as T-cells).	<p>(CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p> <p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these</p>	<p>(CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
				<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred</p>		

				<p>assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below</p>
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158	HNGFR31	562	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screenings, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC)</p>	<p>under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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					and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
159	HNGIJ31	563	Activation of transcription through cAMP response element in immune cells (such as T-cells).	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in	Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred	

				<p>Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.</p>	<p>indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p>
159	HNGIJ31	563	Production of MCP-1	<p>MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the</p>

			<p>are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human</p>	<p>invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity"; "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g.,</p>
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				<p>dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
159	HNGIJ31	563	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>

				<p>(1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
159	HNGIJ31	563	<p>Activation of Skeletal Muscle Cell P13 Kinase Signalling Pathway</p>	<p>Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for P13 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for P13 kinase</p>	<p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred</p>

				<p>activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred</p>
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					<p>indication is diabetes mellitus.</p> <p>An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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					highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.
160	HNGJES0	564	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly

				<p>IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al.,</p>	<p>preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia,</p>
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				<p>"Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
160	HNGJE50	564	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage</p>

				<p>cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or</p>	<p>(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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161	HNGND37	565	Regulation of transcription through the PEPCK promoter in hepatocytes	<p>glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g.,</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as</p>
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				<p>through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine</p>
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162	HNGO112	566	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling	disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"). Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
				A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental	

				<p>pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec; 10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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162	HNGOI12	566	<p>Production of IL-10 and activation of T-cells.</p>	<p>Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology &amp; Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy</p>	<p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.</p>
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163	HNHEU93	567	<p>Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.</p> <p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells.</p> <p>Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
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163	HNHEU93	567	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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163	HNHEU93	567	ICAM in Normal Human Bronchial Epithelium	include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
164	HNHFM14	568	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	
164	HNHFM14	568	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy



			<p>example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec; 10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon,</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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165	HNHFR04	569	Inhibition of adipocyte ERK signaling pathway.	<p>somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC#CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Kinase assay: measures the phosphorylation of Elk-1, an indication of activation of extracellular signal regulated kinase (ERK). ERK pathway regulates cell growth, proliferation and differentiation. Cells were pretreated with SID supernatants for 15-18 hours, and then 100 nM of insulin was added to stimulate ERK kinase. Phosphorylation of Elk-1 was measured after a 20 minute incubation. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art. Cells were differentiated to an adipose-like</p>	associated with insulin resistance.
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165	HNHFR04	569	<p>Activation of transcription through NFKB response element in immune cells (such as EOL1 cells).</p>	<p>state before being used in the screen. See Green et al., Cell 3: 127-133 (1974), the contents of which are herein incorporated by reference in its entirety.</p> <p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures</p>	<p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, and inflammation. Preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), immunological disorders, inflammation and inflammatory disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).</p>
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165	HNHFR04	569	<p>increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFkB element to a reporter gene and binds to the NFkB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils.</p> <p>Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.</p>	<p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the</p>
			<p>Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in</p>	
			<p>Activation of Skeletal Muscle Cell PI3 Kinase Signalling Pathway</p>	

				<p>Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g.,</p>
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					<p>renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred</p>
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165	HNHFR04	569	<p>Activation of transcription through NFKB response element in neuronal cells (such as SKNMC cells).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of neuronal</p>	<p>indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Neurological Diseases and Disorders (e.g. Alzheimer's Disease, Parkinson's Disease, Brain Cancer, Seizures).</p>
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				<p>genes. Exemplary assays for transcription through the NFκB response element that may be used or routinely modified to test NFκB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Gill JS, et al., Neurobiol Dis, 7(4):448-461 (2000); Tamatani M, et al., J Biol Chem, 274(13):8531-8538 (1999); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al., Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Neuronal cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary neuronal cells that may be used according to these assays include the SKNMC neuronal cell line.</p>	
166	HNHNB29	570	Regulation of transcription through the PEPCK promoter in hepatocytes	<p>Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy</p>	



				<p>antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications</p>
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					<p>associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas.</p> <p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate,</p>
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				<p>each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart</p>
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					<p>disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include</p>
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167	HNHOD46	571	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely	neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
				A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the	

				<p>modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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167	HNHOD46	571	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malin, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g.,</p>
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				<p>923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
167	HNHOD46	571	<p>Activation of transcription through serum response element in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998);</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>

				<p>Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below). Additional highly preferred indications are complications associated with insulin resistance.</p>
167	HNHOD46	571	<p>Activation of transcription through cAMP response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP and regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element</p>	<p>Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-</p>

				<p>that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.</p>	<p>mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme</p>
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167	HNHOD46	571	Activation of transcription through serum response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.	Disease, and asthma and allergy. A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for
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167	HNHOD46	571	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated	<p>example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6</p>
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				<p>expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol</p>	<p>production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and</p>
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				<p>158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
167	HNHOD46	571	Production of MIP1alpha	<p>MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating MIP1a production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MIP1a production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related</p>

				<p>assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Erenin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative</p>
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167	HNHOD46	571	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-</p>	<p>disorders and pre-neoplastic conditions; such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia.</p>
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167	HNHOD46	571	<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
			<p>Activation of transcription through NFAT response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as</p>

				<p>functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
HNHOD46	571	Proliferation of pre-adipose cells (such as	Assays for the regulation (i.e. increases or decreases) of viability		

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167	HNHOD46	571	3T3-L1 cells)	<p>and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo<sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.</p>	Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus
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				<p>expression of genes involved in a wide variety of cell functions. Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Genes 15(2):105-117 (1997); and Belkowski et al., J Immunol 161(2):659-665 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.</p>	<p>erythematosis, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune</p>
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167	HNHOD46	571	Activation of transcription through NFAT response in immune cells (such as T-cells).	Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-	reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications
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				<p>14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.</p>	<p>include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
167	HNHOD46	571	<p>Activation of transcription through NFKB response element in immune cells (such as basophils).</p>	<p>This reporter assay measures activation of the NFKB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response</p>	<p>Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as</p>

				<p>element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.</p>	<p>described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
167	HNHOD46	571	<p>Activation of transcription through GAS response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for</p>	<p>Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal,</p>



				<p>transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the MOLT4 cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).</p>	<p>stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma,</p>
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167	HNHOD46	571	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by	arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and
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				reference in its entirety. Exemplary human T cells, such as the MOL.T4, that may be used according to these assays are publicly available (e.g., through the ATCC).	prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.
167	HNHOD46	571	Activation of transcription through serum response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for	A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune

				<p>transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia</p>
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167	HNHOD46	571	Activation of transcription through NFKB response element in immune cells (such as natural killer cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992);		(ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
				Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as		

167	HNHOD46	571	Activation of transcription through API response element in immune cells (such as T-cells).	Assays for the activation of transcription through the API response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to	<p>Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-L cell line, which is a human natural killer cell line established from the peripheral blood of a patient with large granular lymphocytic leukemia. This IL-2 dependent suspension culture cell line has a morphology resembling that of activated NK cells.</p>	<p>described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p> <p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an</p>
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				<p>modulate growth and other cell functions. Exemplary assays for transcription through the API response element that may be used or routinely modified to test API-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1988); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Rellahan et al., J Biol Chem 272(49):30806-30811 (1997); Chang et al., Mol Cell Biol 18(9):4986-4993 (1998); and Fraser et al., Eur J Immunol 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is an IL-2 and IL-4 responsive suspension-culture cell line.</p>	<p>infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted</p>
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167	HNHOD46	571	<p>Activation of transcription through CD28 response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a</p>	<p>organs and tissues, endocarditis, meningitis, and Lyme Disease.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Highly preferred indications include</p>
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				<p>suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma (e.g., metastatic melanoma), renal cell carcinoma (e.g., metastatic renal cell carcinoma), leukemia, lymphoma (e.g., T cell lymphoma), and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. A highly preferred indication includes infection (e.g., AIDS, tuberculosis, infections associated with granulomatous disease, and osteoporosis, and/or as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred indications include suppression of immune reactions to transplanted organs and/or tissues, uveitis, psoriasis, and tropical spastic paraparesis. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular</p>
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167	HNHOD46	571	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al.,	Disorders"). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
				Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as	

				<p>Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).</p>	<p>described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p>
167	HNHOD46	571	<p>Activation of transcription through NFAT response</p>	<p>Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT)</p>	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune</p>

			<p>element in immune cells (such as T-cells).</p>	<p>response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Serfling et al., Biochim Biophys Acta 1498(1):1-18 (2000); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the</p>	<p>Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute</p>
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167	HNHOD46	571	Activation of transcription through NFKB response element in immune cells (such as T-cells).	SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.	lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
				Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-	Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such

				<p>844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>as, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>
167	HNHOD46	571	<p>Activation of transcription through STAT6 response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of</p>	<p>A highly preferred indication is allergy. Another highly preferred indication is asthma. Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include</p>

			<p>multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional</p>
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168	HNTB126	572	Production of IL-8 by endothelial cells (such as Human Umbilical Cord Endothelial Cells).	Assays measuring production of IL-8 are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8. For example, FMAT may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate production and/or secretion of IL-8 from endothelial cells (such as human umbilical vein endothelial cells (HUVEC)). HUVECs are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Endothelial cells play a pivotal role in the initiation and perpetuation of inflammation and secretion of IL-8 may play an important role in recruitment and activation of immune cells such as neutrophils, macrophages, and lymphocytes.	preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include immunological and inflammatory disorders (e.g., such as allergy, asthma, leukemia, etc. and as described below under "Immune Activity", and "Blood-Related Disorders"). Highly preferred indications also include autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), neoplastic disorders (e.g., organ cancers such as lung, liver, colon cancer, and/or as described below under "Hyperproliferative Disorders"), and cardiovascular disorders (e.g., such as described below under "Cardiovascular Disorders"). Preferred indications include thrombosis, bacteremia and sepsis syndrome and consequent complications (such as acute respiratory distress syndrome and systemic ischemia-reperfusion resulting from septic shock), restenosis and atherosclerosis.
168	HNTB126	572	Regulation of apoptosis in pancreatic beta cells.	Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely	A highly preferred indication is diabetes mellitus. An additional highly preferred indication



				<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary</p>	<p>is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred</p>
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169	HNTBL27	573		<p>pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057</p> <p>Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
			<p>Regulation of apoptosis in pancreatic beta cells.</p>	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section</p>

				<p>(2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057</p> <p>Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
169	HNTBL27	573	<p>Production of IL-10 and activation of T-cells.</p>	<p>Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit</p>	<p>Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis,</p>

				production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.	systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.
170	HNTCE26	574	Production of TNF alpha by dendritic cells	TNFα FMAT. Assays for immunomodulatory proteins produced by activated macrophages,	A highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) TNF

				<p>T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFα), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1998); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference</p>	<p>alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal,</p>
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				<p>in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
170	HNTCE26	574	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage</p>

			<p>cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. <i>Endocrinology</i> 1992 130:167.</p>	<p>(e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
HNTCE26	574	Production of ICAM-1	Assays for measuring expression of	Preferred embodiments of the

170				<p>ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used or routinely modified to measure ICAM-1 expression include assays disclosed in: Takacs P, et al, FASEB J, 15(2):279-281 (2001); and, Miyamoto K, et al., Am J Pathol, 156(5):1733-1739 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include microvascular endothelial cells (MVEC).</p>	<p>invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Inflammation, Vascular Disease, Atherosclerosis, Restenosis, and Stroke</p>
171	HNTNC20	575	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting</p>



			<p>or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with</p>
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					<p>diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternately, weight gain. Additional highly</p>
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					<p>preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
172	HNTN101	576	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as</p>

				<p>activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its</p>	<p>described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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172	HNTN101	576	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental</p>
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				<p>for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
172	HNTN101	576	<p>Activation of transcription through serum response element in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include</p>

				<p>routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in</p>	<p>weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyposmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below). Additional highly preferred indications are complications associated with insulin</p>
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172	HNTN101	576	<p>Activation of transcription through GAS response element in immune cells (such as eosinophils).</p>	<p>the art.</p> <p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate gene expression (commonly via STAT transcription factors) involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995); the contents of each of which are herein incorporated by reference in its entirety. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or</p>	<p>resistance.</p> <p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting an eosinophil-mediated immune response and, alternatively, suppressing an eosinophil-mediated immune response.</p>
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				antagonists of the invention) to activate or inhibit activation of immune cells include assays disclosed and/or cited in: Mayumi M., "EoL-1, a human eosinophilic cell line" Leuk Lymphoma; Jun;7(3):243-50 (1992); Bhattacharya S, "Granulocyte macrophage colony-stimulating factor and interleukin-5 activate STAT5 and induce CIS1 mRNA in human peripheral blood eosinophils" Am J Respir Cell Mol Biol; Mar;24(3):312-6 (2001); and, Du J, et al., "Engagement of the CrkL adapter in interleukin-5 signaling in eosinophils" J Biol Chem; Oct 20;275(42):33167-75 (2000); the contents of each of which are herein incorporated by reference in its entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are a type of immune cell important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Increases in GAS mediated transcription in eosinophils is typically a result of STAT activation, normally a direct consequence of interleukin or other cytokine receptor stimulation (e.g. IL3, IL5 or GMCSF).	Highly preferred indications include asthma, allergy, hypersensitivity reactions, and inflammation.
				Assays for the activation of transcription through the NFkB response element are well-known in	
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			<p>element in immune cells (such as EOL1 cells).</p>	<p>the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFkB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFkB element to a reporter gene and binds to the NFkB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used</p>	<p>Preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), immunological disorders, inflammation and inflammatory disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).</p>
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172	HNTN101	576	Regulation of transcription of Malic Enzyme in adipocytes	<p>according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils. Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME<sub>d</sub> identified as putative PPAR response elements. ME promoter may also responds to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>
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172	HNTN101	576	<p>Activation of transcription through GATA-3 response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as</p>

				<p>transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
	HNTN101	576	Activation of transcription through NFAT response	<p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications</p>

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			<p>line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein</p>	<p>include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory</p>
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172	HNTN101	576	Activation of transcription through NFkB response element in immune cells (such as mast cells).	incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.	bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
			This reporter assay measures activation of the NFkB signaling pathway in HMC-1 human mast cell line. Activation of NFkB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFkB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFkB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the	Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications	

				<p>invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al., J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
172	HNTN101	576	<p>Activation of transcription through STAT6 response element in immune cells (such as mast cells).</p>	<p>Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes.</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include hematopoietic and immunological disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), autoimmune diseases</p>



				<p>Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>(e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include hematopoietic and immunological disorders such as arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
172	HNTN101	576	Activation of transcription through NFKB response element in immune	<p>This reporter assay measures activation of the NFKB signaling pathway in Ku812 human basophil cell line. Assays for the activation of</p>	<p>Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an</p>

			<p>transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate</p>	<p>infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
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172	HNTN101	576	<p>Activation of transcription through NFAT response element in immune cells (such as natural killer cells).</p>	<p>Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are</p>	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or</p>
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				publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.	dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
172	HNTN101	576	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and	Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus,



173	Mucle Cell PI3 Kinase Signalling Pathway	<p>example an GSK-3 kinase assay, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine</p>
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					Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine
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					<p>disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and</p>
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174	HOCNF19	578	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein</p>	<p>urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as</p>
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				<p>incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>
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					<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as,</p>
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174	HOCNF19	578	Production of IL-4	<p>IL-4 FMAT. Assays for immunomodulatory proteins secreted by TH2 cells that stimulate B cells, T cells, macrophages and mast cells and promote polarization of CD4+ cells into TH2 cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, stimulate immune cells, modulate immune cell polarization, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-4, and the stimulation of immune cells, such as B cells, T cells, macrophages and mast cells. Such assays that may be used or routinely modified to test immunomodulatory</p>	<p>lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-4 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-4 production. A highly preferred indication includes asthma. A highly preferred indication includes allergy. A highly preferred indication includes rhinitis. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung,</p>
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				<p>activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):277-283 (1994); Yssel et al., Res Immunol 144(8):610-616 (1993); Bagley et al., Nat Immunol 1(3):257-261 (2000); and van der Graaff et al., Rheumatology (Oxford) 38(3):214-220 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
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175	HODDF13	579	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 ( Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional</p>
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175	HODDF13	579	Inhibition of squalene synthetase gene transcription.	<p>as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p> <p>Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.</p>	highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
175	HODDF13	579	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular</p>

				<p>(including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol. 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with</p>	<p>Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
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175	HODDF13	579	Activation of transcription through NFAT response element in immune cells (such as mast cells).	mast cell leukemia, and exhibits many characteristics of immature mast cells. This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol	Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia,
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175	HODDF13	579	<p>Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate,</p>

				be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.	breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
175	HODDF13	579	Activation of Transcription	Assays for activation of transcription are well-known in the art and may be used and routinely modified to assess ability of polypeptides of the invention to inhibit or activate transcription. An example of such an assay follows: Cells were pretreated with SID supernatants or controls for 15-18 hours. SEAP activity was measured after 48 hours. LS174T is an epithelial colon adenocarcinoma cell line. Its tumorigenicity in nude mice make cell line LS174T a model for studies on the mechanism of synthesis and secretion of specific tumoral markers in colon cancer. See, Patan et al., Circ Res, 89(8):732-39 (2001), the contents of which are herein incorporated by reference in its entirety.	
176	HODDN92	580	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6

				<p>induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-</p>	<p>production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as,</p>
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			<p>204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
176	HODDN92	580	<p>Production of MCP-1</p>	<p>MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below</p>

			<p>invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional</p>	<p>under "Infectious Disease"). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as,</p>
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176	HODDN92	580	Production of MIP1 alpha	activities.	<p>leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating MIP1a production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MIP1a production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute</p>
				<p>MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular</p>	

				<p>Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma, and allergy. Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
176	HODDN92	580	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy,</p>



			<p>transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
176	HODDN92	580	Activation of transcription through	<p>This reporter assay measures activation of the GATA-3 signaling</p>

			<p>GATA-3 response element in immune cells (such as mast cells).</p>	<p>pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein</p>	<p>Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS,</p>
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					incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.	granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
176	HODDN92	580	Activation of transcription through NFAT response element in immune cells (such as mast cells).	This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention	Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary	

				<p>(including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
176	HODDN92	580	Activation of Endothelial Cell p38 or JNK Signaling Pathway.	<p>Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the</p>

				<p>antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) the activation of and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy.</p>
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					<p>Highly preferred indications include neoplastic diseases (e.g., as described below under “Hyperproliferative Disorders”), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under “Cardiovascular Disorders”). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi’s sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as,</p>
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					<p>Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury,</p>
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					<p>rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p>
177	HODEJ32	581	Activation of Skeletal Muscle Cell PI3 Kinase	Kinase assay. Kinase assays, for example an GSK-3 kinase assay, for	A highly preferred embodiment of the invention includes a method for



			<p>PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as</p>
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					described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the
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					<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p> <p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications</p>
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178	HOFMQ33	582	Regulation of viability and proliferation of pancreatic beta cells.	<p>Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ohtani KI, et al., Endocrinology, 139(1):172-8 (1998); Krauthelm A, et al, Exp Clin Endocrinol Diabetes, 107 (1):29-34 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these</p>	<p>also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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				assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.	wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
179	HOBY44	583	Activation of Adipocyte ERK Signaling Pathway	Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include	A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative

				<p>the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>
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					<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems</p>
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					including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
180	HOQBJ82	584	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-	



180	HOQBJ82	584	Insulin Secretion	<p>8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious</p>
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				<p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
181	HOSBY40	585	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic</p>

182	HOSDJ25	586	Production of ICAM-1	<p>somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 ( Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p> <p>Assays for measuring expression of ICAM-1 are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate ICAM-1 expression. Exemplary assays that may be used</p>	<p>hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Vascular Disease, Atherosclerosis, Restenosis, Stroke, and Asthma.</p>
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182	HOSD125	586	<p>Activation of transcription through NFAT response element in immune cells (such as natural killer cells).</p>	<p>Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention</p>	<p>or routinely modified to measure ICAM-1 expression include assays disclosed in: Rolfe BE, et al., Atherosclerosis, 149(1):99-110 (2000); Panettieri RA Jr, et al., J Immunol, 154(5):2358-2365 (1995); and, Grunstein MM, et al., Am J Physiol Lung Cell Mol Physiol, 278(6):L1154-L1163 (2000), the contents of each of which is herein incorporated by reference in its entirety. Cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include Aortic Smooth Muscle Cells (AOSMC); such as bovine AOSMC.</p>	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. An additional highly</p>
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				<p>(including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Aramburu et al., J Exp Med 182(3):801-810 (1995); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Fraser et al., Eur J Immunol 29(3):838-844 (1999); and Yeseen et al., J Biol Chem 268(19):14285-14293 (1993), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
182	HOSDJ25	586	Regulation of apoptosis in pancreatic beta cells.	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with</p>

				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used</p>	<p>diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or</p>
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				<p>according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057</p> <p>Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
183	HUCQ17	587	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below</p>

				<p>410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental</p>
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					<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis,</p>
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183	HOUQC17	587	Regulation of proliferation and/or differentiation in immune cells (such as mast cells).	Kinase assays, for example an Elk-1 kinase assay for ERK signal transduction that regulates cell proliferation or differentiation, are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Ali H, et al., J Immunol, 165(12):7215-7223	<p>eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of asthma, allergy, hypersensitivity and inflammation.</p>
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183	HUCQ17	587	<p>Activation of transcription through GATA-3 response element in immune cells (such as mast cells).</p>	<p>(2000); Tam SY, et al., Blood, 90(5):1807-1820 (1997); Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Berra et al., Biochem Pharmacol 60(8):1171-1178 (2000); Gupta et al., Exp Cell Res 247(2):495-504 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Exemplary immune cells that may be used according to these assays include human mast cells such as the HMC-1 cell line.</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma,</p>
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				<p>response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
				<p>Activation of transcription through NFAT response element in immune cells (such as mast cells)</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and</p>

				<p>the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly</p>	<p>inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted</p>
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183	HUCQ17	587			<p>available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo® Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein</p>	organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.
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183	HUCQ17	587	Production of RANTES in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	incorporated by reference in its entirety. RANTES FMAT. Assays for immunomodulatory proteins that induce chemotaxis of T cells, monocytes, and eosinophils are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as RANTES, and the induction of chemotactic responses in immune cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Cocchi et al., Science 270(5243):1811-1815 (1995); and Robinson et al., Clin Exp Immunol 101(3):398-407 (1995), the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may	
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				be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.	
184	HPEAD79	588	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and	A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine



				<p>pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
HP1BO15	589	Regulation of viability	Assays for the regulation of viability	A highly preferred indication is	

185	and proliferation of pancreatic beta cells.	and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell	diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or
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				line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
185	HPIBO15	589	Production of IL-6	IL-6 FMAT. IL-6 is produced by T cells and has strong effects on B cells. IL-6 participates in IL-4 induced IgE production and increases IgA production (IgA plays a role in mucosal immunity). IL-6 induces cytotoxic T cells. Deregulated expression of IL-6 has been linked to autoimmune disease, plasmacytomas, myelomas, and chronic hyperproliferative diseases. Assays for immunomodulatory and differentiation factor proteins produced by a large variety of cells where the expression level is strongly regulated by cytokines, growth factors, and hormones are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and differentiation and modulate T cell proliferation and function. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as	A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-6 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-6 production. A highly preferred indication is the stimulation or enhancement of mucosal immunity. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting a B cell-mediated immune response and alternatively suppressing a B cell-mediated immune response. Highly preferred indications include

				<p>IL-6, and the stimulation and upregulation of T cell proliferation and functional activities. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>inflammation and inflammatory disorders. Additional highly preferred indications include asthma and allergy. Highly preferred indications include neoplastic diseases (e.g., myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, myeloma, plasmacytoma, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below</p>
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186	HPJBI33	590	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may</p>	<p>under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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				<p>be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
187	HPJBK12	591	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>

187	HPJBK12	591			<p>Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
				<p>Regulation of apoptosis of immune cells (such as mast cells).</p>	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate caspase protease-mediated apoptosis in immune cells (such as, for example, in mast cells). Mast</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of asthma, allergy, hypersensitivity and inflammation.</p>





			<p>JNK Signaling Pathway.</p>	<p>regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not</p>	<p>stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) the activation of and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred</p>
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				<p>limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly</p>
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					<p>preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include</p>
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					<p>trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic</p>
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188	HPICL22	592	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g.,</p>	<p>inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension,</p>
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				<p>through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders", immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section</p>
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					<p>below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung,</p>
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189	HPMDK28	593	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al.,	pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
				A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision	



				<p>Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
190	HPRAL78	594	<p>Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes</p>	<p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin</p>	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p>

				<p>production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC)</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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191	HRABA80	595	Insulin Secretion	<p>and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine</p>
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191	HRABA80	595	Activation of Endothelial Cell ERK Signaling Pathway.	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for</p>

				<p>invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Berra et al., Biochem Pharmacol 60(8):1171-1178 (2000); Gupta et al., Exp Cell Res 247(2):495-504 (1999); Chang and Karn, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are endothelial cells which line venous blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) endothelial cell activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell differentiation. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting</p>
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					<p>angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit</p>
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					<p>angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular</p>
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					<p>disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vasculitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include</p>
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192	HRACD15	596	Regulation of transcription of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME <sub>d</sub> identified as putative PPARG response elements. ME promoter may also respond to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999);	inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.  A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g.,
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				<p>Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
192	HRACD15	596	<p>Activation of T-Cell p38 or JNK Signaling Pathway.</p>	<p>Kinase assay. JNK and p38 kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit immune cell (e.g. T-cell) proliferation, activation, and apoptosis. Exemplary assays for JNK and p38 kinase activity that may be used or routinely modified to test JNK and p38 kinase-induced activity</p>	<p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), and infection (e.g., an infectious disease as described below under "Infectious Disease"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and</p>

				<p>of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9): 1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension-culture cell line with cytotoxic activity.</p>	<p>immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include arthritis, asthma, AIDS, allergy, anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, granulomatous disease, inflammatory bowel disease, sepsis, psoriasis, suppression of immune reactions to transplanted organs and tissues, endocarditis, meningitis, and Lyme Disease.</p>
192	HRACD15	596	Regulation of apoptosis of immune cells (such as mast cells).	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention,</p>

				<p>(including antibodies and agonists or antagonists of the invention) to regulate caspase protease-mediated apoptosis in immune cells (such as, for example, in mast cells). Mast cells are found in connective and mucosal tissues throughout the body, and their activation via immunoglobulin E -antigen, promoted by T helper cell type 2 cytokines, is an important component of allergic disease. Dysregulation of mast cell apoptosis may play a role in allergic disease and mast cell tumor survival. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity induced by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Masuda A, et al., J Biol Chem, 276(28):26107-26113 (2001); Yeatman CF 2nd, et al., J Exp Med, 192(8):1093-1103 (2000); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary immune cells that may be used</p>	<p>and/or treatment of asthma, allergy, hypersensitivity and inflammation.</p>
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193	HRAC135	597	Regulation of Malic Enzyme in hepatocytes	<p>according to these assays include mast cells such as the HMC human mast cell line.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME<sub>d</sub> identified as putative PPAR response elements. ME promoter may also respond to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyposmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially</p>
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				and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
193	HRAC135	597	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may	Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate,

194	HRGBL78	598		<p>be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66</p>	<p>breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
				<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the</p>	

				<p>(1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
195	HROAJ39	599	<p>Stimulation of Calcium Flux in pancreatic beta cells.</p>	<p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>	



				<p>factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and</p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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196	HROBD68	600	Regulation of apoptosis in pancreatic beta cells.	<p>Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett. 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int. 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially</p>
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			are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
197	HSAWD74	601	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	<p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma,</p>

				<p>expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a</p>	<p>cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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197	HSAWD74	601	Activation of transcription through NFAT response element in immune cells (such as mast cells).	continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,
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				<p>6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
197	HSAWD74	601	<p>Proliferation of pre-adipose cells (such as 3T3-L1 cells)</p>	<p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo<sup>®</sup> Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in</p>	

198	HSDEK49	602		<p>culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly</p>
				<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and</p>	<p>Activation of serum response element in immune cells (such as T-cells).</p>

				<p>Black et al., Virus Genes 12(2): 105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis,</p>
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198	HSDEK49	602	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME <sub>d</sub> identified as putative PPAR response elements. ME promoter may also respond to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999);	meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").  A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g.,
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199	HSDFJ26	603	<p>Regulation of transcription through the PEPCK promoter in hepatocytes</p>	<p>Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and</p>

				<p>Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988);  Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas.</p>
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200	HSDJA15	604	Activation of Adipocyte P13 Kinase Signalling Pathway	Kinase assay. Kinase assays, for example an GSK-3 assays, for P13 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely	<p>Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing</p>
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				<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p>	A
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					highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional
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					highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternately, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
200	HSD1A15	604	Activation of transcription through serum response element	Assays for the activation of transcription through the Serum Response Element (SRE) are well-	A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha

			<p>known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic,</p>
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200	HSDJA15	604	<p>Activation of transcription through GATA-3 response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related</p>	<p>esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p>
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				<p>polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the</p>	<p>Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
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200	HSDJA15	604	Production of IL-5	peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells. IL-5 FMAT. Assays for immunomodulatory proteins secreted by TH2 cells, mast cells, basophils, and eosinophils that stimulate eosinophil function and B cell Ig production and promote polarization of CD4+ cells into TH2 cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, stimulate immune cell function, modulate B cell Ig production, modulate immune cell polarization, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as IL-5, and the stimulation of eosinophil function and B cell Ig production. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach"	A highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-5 production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-5 production. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) immunoglobulin production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) immunoglobulin production. A highly preferred indication includes allergy. A highly preferred indication includes asthma. A highly preferred indication includes rhinitis. An additional highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus
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				<p>Chapter 6:138-160 (2000); Ohshima et al., Blood 92(9):3338-3345 (1998); Jung et al., Eur J Immunol 25(8):2413-2416 (1995); Mori et al., J Allergy Clin Immunol 106(1 Pt 2):558-564 (2000); and Koning et al., Cytokine 9(6):427-436 (1997), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>erythematosis, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
201	HSDIM31	605	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte</p>

			<p>cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed</p>	<p>proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below</p>
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				through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g.,
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					<p>infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for</p>
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202	HSDSB09	606	Regulation of transcription via DMEF1 response element in adipocytes and pre-adipocytes	<p>Assays for the regulation of transcription through the DMEF1 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the DMEF1 response element in a reporter construct (such as that containing the GLUT4 promoter) and to regulate insulin production. The DMEF1 response element is present in the GLUT4 promoter and binds to MEF2 transcription factor and another transcription factor that is required for insulin regulation of Glut4 expression in skeletal muscle. GLUT4 is the primary insulin-responsive glucose transporter in fat and muscle tissue. Exemplary assays that may be used or routinely modified to test for DMEF1 response element activity (in adipocytes and pre-adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Thai, M.V., et al., J Biol Chem, 273(23):14285-92 (1998); Mora, S., et al., J Biol Chem, 275(21):16323-8 (2000); Liu, M.L., et al., J Biol Chem, 269(45):28514-21 (1994); "Identification of a 30-base pair</p>	<p>example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyposmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). An</p>
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				<p>regulatory element and novel DNA binding protein that regulates the human GLUT4 promoter in transgenic mice", J Biol Chem. 2000 Aug 4;275(31):23666-73; Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Adipocytes and pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary cells that may be used according to these assays include the mouse 3T3-L1 cell line which is an adherent mouse preadipocyte cell line. Mouse 3T3-L1 cells are a continuous substrain of 3T3 fibroblasts developed through clonal isolation. These cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
202	HSDSB09	606	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease</p>

				<p>wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain</p>	<p>(e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
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202	HSDSB09	606	Activation of transcription through serum response element in pre-adipocytes.	<p>of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p> <p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated.</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the</p>
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202	HSDSB09	606	<p>Activation of transcription through serum response element in immune cells (such as T-cells).</p>	<p>Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p> <p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by</p>	<p>"Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below). Additional highly preferred indications are complications associated with insulin resistance.</p> <p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage</p>
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				<p>reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred</p>
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202	HSDSB09	606	Regulation of transcription of Malic Enzyme in adipocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME <sub>d</sub> identified as putative PPAR response elements. ME promoter may also respond to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Lipenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988);	indication is infection (e.g., an infectious disease as described below under "Infectious Disease").  A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyposmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially
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				and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.	of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
202	HSDSB09	606	SEAP in HIB/CRE		
202	HSDSB09	606	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the

202	HSDSB09	606	Activation of transcription through GATA-3 response element in immune cells (such as mast cells).	<p>assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT T15 Cells. HIT T15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription</p>	<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory</p>
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				<p>through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3 response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that</p>	<p>disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia,</p>
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202	HSDSB09	606	Activation of transcription through NFAT response element in immune cells (such as mast cells).	<p>may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol</p>	<p>hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
				<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-</p>	

				<p>216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
202	HDSB09	606	<p>Activation of transcription through NFKB response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the NFKB signaling pathway in HMC-1 human mast cell line. Activation of NFKB in mast cells has been linked to production of certain cytokines, such as IL-6 and IL-9. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or</p>	<p>Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications</p>

202	HSDSB09	606	Activation of transcription through STAT6 response	Assays for the activation of transcription through the Signal Transducers and Activators of	antagonists of the invention) to regulate NFkB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFkB response element that may be used or routinely modified to test NFkB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Stassen et al, J Immunol 166(7):4391-8 (2001); and Marquardt and Walker, J Allergy Clin Immunol 105(3):500-5 (2000), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.	also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".	Highly preferred indications include allergy, asthma, and rhinitis. Additional highly preferred
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			<p>element in immune cells (such as mast cells).</p>	<p>Transcription (STAT6) response element in immune cells (such as in the human HMC-1 mast cell line) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Sherman, Immunol Rev 179:48-56 (2001); Malaviya and Uckun, J Immunol 168:421-426 (2002); Masuda et al., J Biol Chem 275(38):29331-29337 (2000); and Masuda et al., J Biol Chem 276:26107-26113 (2001), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these</p>	<p>indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include hematopoietic and immunological disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include hematopoietic and immunological disorders such as arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia,</p>
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202	HSDSB09	606	Stimulation of insulin secretion from pancreatic beta cells.	assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.  Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated	psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.  A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired
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				<p>by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
202	HSDSB09	606	<p>Activation of transcription through NFKB response element in immune cells (such as basophils).</p>	<p>This reporter assay measures activation of the NFKB signaling pathway in Ku812 human basophil cell line. Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes.</p> <p>Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies</p>	<p>Highly preferred indication includes allergy, asthma, and rhinitis. Additional highly preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include neoplastic</p>

				<p>and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Marone et al, Int Arch Allergy Immunol 114(3):207-17 (1997), the contents of each of which are herein incorporated by reference in its entirety. Basophils that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human basophil cell lines that may be used according to these assays include Ku812, originally established from a patient with chronic myelogenous leukemia. It is an immature prebasophilic cell line that can be induced to differentiate into mature basophils.</p>	<p>diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include neoplasms and cancer, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, urinary tract cancers and as described below under "Hyperproliferative Disorders".</p>
202	HSDSB09	606	<p>Activation of transcription through serum response element in immune cells (such as natural killer cells).</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate serum response factors and modulate the expression of genes involved in growth and upregulate the function of growth-related genes in many cell types. Exemplary assays for transcription through the SRE that</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis,</p>



			<p>may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Benson et al., J Immunol 153(9):3862-3873 (1994); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the NK-YT cell line, which is a human natural killer cell line with cytolytic and cytotoxic activity.</p>	<p>systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple</p>
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202	HDSB09	606	<p>Activation of transcription through STAT6 response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Signal Transducers and Activators of Transcription (STAT6) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT6 transcription factors and modulate the expression of multiple genes. Exemplary assays for transcription through the STAT6 response element that may be used or routinely modified to test STAT6 response element activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol</p>	<p>myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred indication is allergy. Another highly preferred indication is asthma. Additional highly preferred indications include inflammation and inflammatory disorders.</p> <p>Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders").</p> <p>Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below).</p> <p>Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders").</p>
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203	HSHAX21	607	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Georas et al., Blood 92(12):4529-4538 (1998); Moffatt et al., Transplantation 69(7):1521-1523 (2000); Curiel et al., Eur J Immunol 27(8):1982-1987 (1997); and Masuda et al., J Biol Chem 275(38):29331-29337 (2000), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the SUPT cell line, which is a suspension culture of IL-2 and IL-4 responsive T cells.</p>	<p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of</p>
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				<p>agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below</p>
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					<p>under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication</p>
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203	HSHAX21	607	Production of MIP1alpha	MIP-1alpha FMAT. Assays for immunomodulatory proteins produced by activated dendritic cells	<p>is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating MIP 1a production.</p>
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				<p>that upregulate monocyte/macrophage and T cell chemotaxis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate chemotaxis, and modulate T cell differentiation. Exemplary assays that test for immunomodulatory proteins evaluate the production of chemokines, such as macrophage inflammatory protein 1 alpha (MIP-1a), and the activation of monocytes/macrophages and T cells. Such assays that may be used or routinely modified to test immunomodulatory and chemotaxis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); Drakes et al., Transp Immunol 8(1):17-29 (2000); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human</p>	<p>An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MIP1a production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease"). Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma, and allergy. Preferred indications also include</p>
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				<p>dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
203	HSHAX21	607	<p>Production of TNF alpha by dendritic cells</p>	<p>TNFα FMAT. Assays for immunomodulatory proteins produced by activated macrophages, T cells, fibroblasts, smooth muscle, and other cell types that exert a wide variety of inflammatory and cytotoxic effects on a variety of cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, modulate inflammation and cytotoxicity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines such as tumor necrosis factor alpha (TNFα), and the induction or inhibition of an inflammatory or cytotoxic response. Such assays that may be used or</p>	<p>A highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) TNF alpha production. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated</p>



				<p>routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Verhasselt et al., Eur J Immunol 28(11):3886-3890 (1998); Dahlen et al., J Immunol 160(7):3585-3593 (1998); Verhasselt et al., J Immunol 158:2919-2925 (1997); and Nardelli et al., J Leukoc Biol 65:822-828 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus,</p>
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203	HSHAX21	607	Activation of transcription through NFKB response element in immune cells (such as T-cells).	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Black et al., Virus Gnes 15(2):105-117 (1997); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the MOLT4,	endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").
				Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach,	

				that may be used according to these assays are publicly available (e.g., through the ATCC).	brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.
204	HSIDJ81	608	Insulin Secretion	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental

				<p>for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATCC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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204	HSIDJ81	608	<p>Activation of transcription through NFKB response element in neuronal cells (such as SKNMC cells).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of neuronal genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Gill JS, et al., Neurobiol Dis, 7(4):448-461 (2000); Tamatani M, et al., J Biol Chem, 274(13):8531-8538 (1999); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Neuronal cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary neuronal cells</p>	<p>Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in detection, diagnosis, prevention, and/or treatment of Neurological Diseases and Disorders (e.g. Alzheimer's Disease, Parkinson's Disease, Brain Cancer, Seizures).</p>
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205	HSJBQ79	609	Activation of Adipocyte ERK Signaling Pathway	<p>that may be used according to these assays include the SKNMC neuronal cell line.</p> <p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel</p>
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				<p>mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders", immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine</p>
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					<p>disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach,</p>
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206	HSKDA27	610	Production of GM-CSF	<p>GM-CSF FMAT. GM-CSF is expressed by activated T cells, macrophages, endothelial cells, and fibroblasts. GM-CSF regulates differentiation and proliferation of granulocytes- macrophage progenitors and enhances antimicrobial activity in neutrophils, monocytes and macrophage. Additionally, GM-CSF plays an important role in the differentiation of dendritic cells and monocytes, and increases antigen presentation. GM-CSF is considered to be a proinflammatory cytokine. Assays for immunomodulatory proteins that promote the production of GM-CSF are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation and modulate the growth and differentiation of leukocytes. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as GM-CSF, and the activation</p>	<p>brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating the production of GM-CSF. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of GM-CSF. Highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., as described below under "Infectious Disease". Highly preferred indications include blood disorders (e.g., neutropenia (and the prevention of neutropenia (e.g., in HIV infected patients), and/or as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include asthma. Highly preferred</p>
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				<p>of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Ye et al., J Leukoc Biol (58(2):225-233, the contents of each of which are herein incorporated by reference in its entirety. Natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC) or may be isolated using techniques disclosed herein or otherwise known in the art. Natural killer (NK) cells are large granular lymphocytes that have cytotoxic activity but do not bind antigen. NK cells show antibody-independent killing of tumor cells and also recognize antibody bound on target cells, via NK Fc receptors, leading to cell-mediated cytotoxicity.</p>	<p>indications include neoplastic diseases (e.g., leukemia (e.g., acute lymphoblastic leukemia, and acute myelogenous leukemia), lymphoma (e.g., non-Hodgkin's lymphoma and Hodgkin's disease), and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications include: suppression of immune reactions to transplanted organs and tissues (e.g., bone marrow transplant); accelerating myeloid recovery; and mobilizing hematopoietic progenitor cells. Preferred indications include boosting a T cell-mediated immune response, and alternatively, suppressing a T cell-mediated immune response. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory</p>
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206	HSKDA27	610	Regulation of apoptosis in pancreatic beta cells.	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett, 455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J</p>	<p>bowel disease, sepsis, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and allergy.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as</p>
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				<p>Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057 Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
207	HSKGN81	611	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental</p>

			<p>for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et al., Journal of Biomolecular Screenings, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
208	HSKNB56	612	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for</p>

				<p>the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate</p>	<p>inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and</p>
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				<p>differentiation conditions known in the art.</p> <p>Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly</p>
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					<p>of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
	HSNAD72	613	Stimulation of insulin	Assays for measuring secretion of	A highly preferred indication is



			<p>secretion from pancreatic beta cells.</p>	<p>insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells</p>	<p>diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity</p>
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210	HSNMC45	614	Stimulation of Calcium Flux in pancreatic beta cells.	are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
				Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al.,	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision

				<p>Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
211	HSQFP66	615	Stimulation of insulin secretion from pancreatic beta cells.	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p>

				<p>also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. <i>Endocrinology</i> 1992 130:167.</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
212	HSRFZ57	616	Regulation of transcription through	<p>Assays for the regulation of transcription through the FAS</p>	<p>A highly preferred indication is diabetes mellitus. An</p>

		<p>the FAS promoter element in hepatocytes</p>	<p>promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 ( Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may</p>	<p>additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with</p>
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212	HSRFZ57	616	Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))	<p>be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p> <p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-I expression in endothelial cells. Endothelial cells are cells that line blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation. Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUVEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and</p>	<p>obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
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213	HSUBW09	617	Regulation of transcription through the FAS promoter element in hepatocytes	<p>inflammatory responses.</p> <p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 ( Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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				used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.	contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
213	HSUBW09	617	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824 (1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	
214	HSVBU91	618	Activation of transcription through cAMP response element (CRE) in pre-adipocytes.	Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a	A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease



				<p>wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain</p>	<p>(e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
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214	HSVBU91	618	Activation of Hepatocyte ERK Signaling Pathway	of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	<p>A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell differentiation. A highly preferred embodiment of the invention includes a method for activating hepatocyte cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating hepatocyte cells. Highly preferred indications include disorders of the liver and/or endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described</p>
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				<p>liver hepatoma cells that may be used according to these assays include H4Ile cells, which are known to respond to glucocorticoids, insulin, or cAMP derivatives.</p>	<p>below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section</p>
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					<p>below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p> <p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include, hepatitis, jaundice, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism.</p> <p>Additional highly preferred indications include neoplasms and cancers, such as, hepatocarcinomas, other liver cancers, and colon and pancreatic cancer. Preferred indications also include prostate,</p>
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214	HSVBU91	618	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., <i>Endocr J</i>, 47(3):261-9 (2000); Salapatek, A.M., et al., <i>Mol Endocrinol</i>, 13(8):1305-17 (1999); Filipsson, K., et al., <i>Ann N Y Acad Sci</i>, 865:441-4 (1998); Olson, L.K., et al., <i>J Biol Chem</i>, 271(28):16544-52 (1996); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>,</p>	<p>breast, lung, esophageal, stomach, brain, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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				<p>4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
214	HSVBU91	618	<p>Activation of transcription through CD28 response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the CD28 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate IL-2 expression in T cells. Exemplary assays for transcription through the CD28 response element that may be used or routinely modified to test CD28-response element activity of polypeptides of</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating T cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting T cell proliferation. A highly preferred embodiment of the invention includes a method for activating T cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating T cells. A highly</p>

				<p>the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); McGuire and Iacobelli, J Immunol 159(3):1319-1327 (1997); Parra et al., J Immunol 166(4):2437-2443 (2001); and Butscher et al., J Biol Chem 3(1):552-560 (1998), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.</p>	<p>preferred embodiment of the invention includes a method for stimulating (e.g., increasing) IL-2 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) IL-2 production. Additional highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. An additional highly preferred indication includes infection (e.g., AIDS, and/or as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, renal cell carcinoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma (e.g., metastatic melanoma), renal cell carcinoma (e.g., metastatic renal cell carcinoma), leukemia, lymphoma (e.g., T cell lymphoma), and prostate, breast, lung, colon, pancreatic,</p>
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				<p>esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. A highly preferred indication is infection (e.g., tuberculosis, infections associated with granulomatous disease, and osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). A highly preferred indication is AIDS. Additional highly preferred indications include suppression of immune reactions to transplanted organs and/or tissues, uveitis, psoriasis, and tropical spastic paraparesis. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
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215	HSXGI47	619	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as</p>
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				<p>described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
			<p>which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	
215	HSXGI47	619	<p>Proliferation of pre-adipose cells (such as 3T3-L1 cells)</p>	<p>Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo® Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a</p>

215	HSXGI47	619	Activation of Skeletal Muscle Cell PI3 Kinase Signalling Pathway	continuous substrain of 3T3 fibroblast cells developed through clonal isolation. Cells were differentiated to an adipose-like state before being used in the screen. See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.	<p>A highly preferred embodiment of the invention includes a method for increasing muscle cell survival. An alternative highly preferred embodiment of the invention includes a method for decreasing muscle cell survival. A preferred embodiment of the invention includes a method for stimulating muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell proliferation. In a specific embodiment, skeletal muscle cell proliferation is inhibited. A preferred embodiment of the invention includes a method for stimulating muscle cell differentiation. In a specific embodiment, skeletal muscle cell differentiation is stimulated. An alternative highly preferred embodiment of the invention includes a method for inhibiting muscle cell differentiation. In a</p>
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				<p>publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>specific embodiment, skeletal muscle cell differentiation is inhibited. Highly preferred indications include disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel</p>
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					<p>blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal system including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include: myopathy,</p>
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216	HSYAZ63	620	Activation of Adipocyte PI3 Kinase Signalling Pathway	<p>Kinase assay. Kinase assays, for example an GSK-3 assays, for PI3 kinase signal transduction that regulate glucose metabolism and cell survival are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit glucose metabolism and cell survival. Exemplary assays for PI3 kinase activity that may be used or routinely modified to test PI3 kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in</p>	<p>atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for increasing adipocyte survival. An alternative highly preferred embodiment of the invention includes a method for decreasing adipocyte survival. A preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention</p>
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				<p>Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Nikoulina et al., Diabetes 49(2):263-271 (2000); and Schreyer et al., Diabetes 48(8):1662-1666 (1999), the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>includes a method for inhibiting adipocyte differentiation. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"), blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>
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					<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p>
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					Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Highly preferred indications include neoplasms and cancer, such as, lipoma, liposarcoma, lymphoma, leukemia and breast, colon, and kidney cancer. Additional highly preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
216	HSYAZ63	620	Activation of transcription through GAS response element in immune cells (such as T-cells).	Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-	Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-

				<p>response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary human T cells, such as the SUPT cell line, that may be used according to these assays are publicly available (e.g., through the ATCC).</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity"; "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune</p>
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217	HSYBG37	621	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these</p>	<p>reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood</p>
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			assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the
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					<p>"Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include</p>
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217	HSYBG37	621	Activation of JNK Signaling Pathway in immune cells (such as eosinophils).	<p>Kinase assay. JNK kinase assays for signal transduction that regulate cell proliferation, activation, or apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and apoptosis. Exemplary assays for JNK kinase activity that may be used or routinely modified to test JNK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Gupta et al., Exp Cell Res 247(2): 495-504 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein</p>	<p>melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting or inhibiting immune cell proliferation. Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include boosting an eosinophil-mediated immune response, and suppressing an eosinophil-mediated immune response.</p>
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				<p>incorporated by reference in its entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate signal transduction, cell proliferation, activation, or apoptosis in eosinophils include assays disclosed and/or cited in: Zhang JP, et al., "Role of caspases in dexamethasone-induced apoptosis and activation of c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in human eosinophils" Clin Exp Immunol; Oct;122(1):20-7 (2000); Hebestreit H, et al., "Disruption of fas receptor signaling by nitric oxide in eosinophils" J Exp Med; Feb 2;187(3):415-25 (1998); J Allergy Clin Immunol 1999 Sep;104(3 Pt 1):565-74; and, Sousa AR, et al., "In vivo resistance to corticosteroids in bronchial asthma is associated with enhanced phosphorylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation" J Allergy Clin</p>
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218	HTADW91	622	Activation of Hepatocyte ERK Signaling Pathway	Immunol; Sep;104(3 Pt 1):565-74 (1999); the contents of each of which are herein incorporated by reference in its entirety.  Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat liver hepatoma cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat liver hepatoma cells that may be used according to these assays include	A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating hepatocyte cell differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting hepatocyte cell differentiation. A highly preferred embodiment of the invention includes a method for activating hepatocyte cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of and/or inactivating hepatocyte cells. Highly preferred indications include disorders of the liver and/or endocrine disorders (e.g., as described below under "Endocrine Disorders"). Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or
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					<p>H4Ile cells, which are known to respond to glucocorticoids, insulin, or cAMP derivatives.</p>	<p>"Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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					<p>and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hepatitis, jaundice, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism. Additional highly preferred indications include neoplasms and cancers, such as, hepatocarcinomas, other liver cancers, and colon and pancreatic cancer. Preferred indications also include prostate, breast, lung, esophageal, stomach, brain, and urinary cancer. Other</p>
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219	HTAEE28	623	Protection from Endothelial Cell Apoptosis.	<p>Caspase Apoptosis Rescue. Assays for caspase apoptosis rescue are well known in the art and may be used or routinely modified to assess the ability of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to inhibit caspase protease-mediated apoptosis. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis rescue of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Romeo et al., Cardiovasc Res 45(3): 788-794 (2000); Messmer et al., Br J Pharmacol 127(7): 1633-1640 (1999); and J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (bAEC), which are an example of endothelial cells which line blood</p>	<p>preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating</p>
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				<p>vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders").</p> <p>Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate</p>
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					<p>angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such</p>
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					<p>as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vasculitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and</p>
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219	HTAEE28	623	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-</p>	<p>immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision</p>
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220	HTDAF28	624	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention</p>
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			<p>ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a</p>
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					<p>complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight</p>

					gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
					Assays for the regulation of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the
					Regulation of viability and proliferation of pancreatic beta cells.
					625
					HTECC05
221					A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy

				<p>invention) to regulate viability and proliferation of pancreatic beta cells. For example, the Cell Titer-Glo luminescent cell viability assay measures the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. Exemplary assays that may be used or routinely modified to test regulation of viability and proliferation of pancreatic beta cells by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Friedrichsen BN, et al., Mol Endocrinol, 15(1):136-48 (2001); Huotari MA, et al., Endocrinology, 139(4):1494-9 (1998); Hugl SR, et al., J Biol Chem 1998 Jul 10;273(28):17771-9 (1998), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p>	<p>and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin</p>
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222	HTEEB42	626	Regulation of transcription of Malic Enzyme in hepatocytes	<p>References: Asfari et al. Endocrinology 1992 130:167.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DRI)-like elements MEp and ME<sub>d</sub> identified as putative PPAR response elements. ME promoter may also respond to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in</p>	<p>resistance.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal</p>
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				<p>Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
223	HTEFU65	627	<p>Activation of transcription through cAMP response element (CRE) in pre-adipocytes.</p>	<p>Assays for the activation of transcription through the cAMP response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to increase cAMP, regulate CREB transcription factors, and modulate expression of genes involved in a wide variety of cell functions. For example, a 3T3-L1/CRE reporter assay may be used to identify factors that activate the cAMP signaling pathway. CREB plays a major role in adipogenesis, and is involved in differentiation into adipocytes. CRE contains the binding sequence for the</p>	<p>A highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. An additional highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>

				<p>transcription factor CREB (CRE binding protein). Exemplary assays for transcription through the cAMP response element that may be used or routinely modified to test cAMP-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Reusch et al., Mol Cell Biol 20(3):1008-1020 (2000); and Klemm et al., J Biol Chem 273:917-923 (1998), the contents of each of which are herein incorporated by reference in its entirety. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). Additional highly preferred indications are complications associated with insulin resistance.</p>
223	HTEFU65	627	Regulation of transcription of Malic	Assays for the regulation of transcription of Malic Enzyme are	A highly preferred indication is diabetes mellitus. An

			Enzyme in hepatocytes	<p>well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME<sub>d</sub> identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be</p>	<p>additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with</p>
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				used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
223	HTEFU65	627	Myoblast cell proliferation	Assays for muscle cell proliferation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit myoblast cell proliferation. Exemplary assays for myoblast cell proliferation that may be used or routinely modified to test activity of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) include, for example, assays disclosed in: Soeta, C., et al. "Possible role for the c-ski gene in the proliferation of myogenic cells in regenerating skeletal muscles of rats" Dev Growth Differ Apr;43(2):155-64 (2001); Ewton DZ, et al., "IGF binding proteins-4, -5 and -6 may play specialized roles during L6 myoblast	Highly preferred indications include diabetes, myopathy, muscle cell atrophy, cancers of muscle (such as, rhabdomyoma, and rhabdosarcoma), cardiovascular disorders (such as congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, vascular disease, and also as described below under "Cardiovascular Disorders"), stimulating myoblast proliferation, and inhibiting myoblast proliferation.

				proliferation and differentiation" J Endocrinol Mar;144(3):539-53 (1995); and, Pampusch MS, et al., "Effect of transforming growth factor beta on proliferation of L6 and embryonic porcine myogenic cells" J Cell Physiol Jun;143(3):524-8 (1990); the contents of each of which are herein incorporated by reference in their entirety. Exemplary myoblast cells that may be used according to these assays include the rat myoblast L6 cell line. Rat myoblast L6 cells are an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuse to form multinucleated myotubes and striated fibers after culture in differentiation media.	
223	HTEFU65	627	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	
	HTEFU65	627	Production of	IFNgamma FMAT. IFNg plays a	A highly preferred embodiment

223			IFNgamma using a T cells	<p>central role in the immune system and is considered to be a proinflammatory cytokine. IFNγ promotes TH1 and inhibits TH2 differentiation; promotes IgG2a and inhibits IgE secretion; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNγ), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al.,</p>	<p>of the invention includes a method for stimulating the production of IFNγ. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNγ. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include</p>
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			<p>"Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Human T cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human T cells are primary human lymphocytes that mature in the thymus and express a T Cell receptor and CD3, CD4, or CD8. These cells mediate humoral or cell-mediated immunity and may be preactivated to enhance responsiveness to immunomodulatory factors.</p>	<p>neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.</p>
223	HTEFU65	627	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy).</p>

				<p>also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. <i>Endocrinology</i> 1992 130:167.</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
224	HTEGA76	628	Activation of Adipocyte ERK	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for</p>	<p>A highly preferred embodiment of the invention includes a method</p>

			<p>ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of</p>	<p>for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune</p>
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				<p>3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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					<p>wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-</p>
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224	HTEGA76	628	Endothelial Cell Apoptosis	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Induction of apoptosis in endothelial cells supporting the vasculature of tumors is associated with tumor regression due to loss of tumor blood supply. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (BAEC), which are an example</p>	<p>neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention</p>
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				<p>of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>	<p>includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under “Hyperproliferative Disorders”), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under “Cardiovascular Disorders”). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi’s sarcoma, and retinal disorders.</p>
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					<p>Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic</p>
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					<p>lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vascularitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p>
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225	HTEJN13	629	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity",</p>
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				<p>adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>"Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision</p>
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					<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other</p>
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225	HTEJN13	629	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-12824(1993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.	preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.
226	HTLP17	630	Regulation of transcription through the PEPCK promoter in hepatocytes	Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel



				<p>hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4IIE cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include glycogen storage</p>
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					<p>disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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226	HTELP17	630	Stimulation of Calcium Flux in pancreatic beta cells.	<p>Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium. Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the</p>	<p>and/or dysplasia. A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's</p>
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227	HTELS08	631		<p>ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
			<p>Regulation of transcription through the PEPCK promoter in hepatocytes</p>	<p>Assays for the regulation of transcription through the PEPCK promoter are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the PEPCK promoter in a reporter construct and regulate liver gluconeogenesis. Exemplary assays for regulation of transcription through the PEPCK promoter that may be used or routinely modified to test for PEPCK promoter activity (in hepatocytes) of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis,</p>

				<p>Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Lochhead et al., Diabetes 49(6):896-903 (2000); and Yeagley et al., J Biol Chem 275(23):17814-17820 (2000), the contents of each of which is herein incorporated by reference in its entirety. Hepatocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary liver hepatoma cells that may be used according to these assays include H4Ile cells, which contain a tyrosine amino transferase that is inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., an infectious diseases or disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include glycogen storage disease (e.g., glycogenoses), hepatitis, gallstones, cirrhosis of the liver, degenerative or necrotic liver disease, alcoholic liver diseases, fibrosis, liver regeneration, metabolic</p>
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227	HTELS08	631	Inhibition of squalene synthetase gene transcription.	Reporter Assay: construct contains regulatory and coding sequence of squalene synthetase, the first specific enzyme in the cholesterol	<p>disease, dyslipidemia and cholesterol metabolism, and hepatocarcinomas. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), infection (e.g., an infectious disease and/or disorder as described below under "Infectious Disease"), endocrine disorders (e.g., as described below under "Endocrine Disorders"), and neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases").</p> <p>Additional preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders").</p> <p>Preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, and urinary cancer. A highly preferred indication is liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
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228	HTLEP53	632	Endothelial Cell Apoptosis	<p>biosynthetic pathway. See Jiang, et al., J. Biol. Chem. 268:12818-128241(993), the contents of which are herein incorporated by reference in its entirety. Cells were treated with SID supernatants, and SEAP activity was measured after 72 hours. HepG2 is a human hepatocellular carcinoma cell line (ATCC HB-8065). See Knowles et al., Science. 209:497-9 (1980), the contents of which are herein incorporated by reference in its entirety.</p> <p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Induction of apoptosis in endothelial cells supporting the vasculature of tumors is associated with tumor regression due to loss of tumor blood supply. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating endothelial cell growth. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell growth. A highly preferred embodiment of the invention includes a method for stimulating endothelial cell proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting endothelial cell proliferation. A highly preferred embodiment of the invention includes a method for stimulating apoptosis of endothelial cells. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., decreasing) apoptosis of endothelial cells. A highly preferred embodiment of the invention</p>
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				<p>includes a method for stimulating angiogenesis. An alternative highly preferred embodiment of the invention includes a method for inhibiting angiogenesis. A highly preferred embodiment of the invention includes a method for reducing cardiac hypertrophy. An alternative highly preferred embodiment of the invention includes a method for inducing cardiac hypertrophy. Highly preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), and disorders of the cardiovascular system (e.g., heart disease, congestive heart failure, hypertension, aortic stenosis, cardiomyopathy, valvular regurgitation, left ventricular dysfunction, atherosclerosis and atherosclerotic vascular disease, diabetic nephropathy, intracardiac shunt, cardiac hypertrophy, myocardial infarction, chronic hemodynamic overload, and/or as described below under "Cardiovascular Disorders"). Highly preferred indications include cardiovascular, endothelial and/or angiogenic disorders (e.g., systemic disorders that affect vessels such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins and/or lymphatics). Highly preferred are</p>
				<p>(1996); the contents of each of which are herein incorporated by reference in its entirety. Endothelial cells that may be used according to these assays are publicly available (e.g., through commercial sources). Exemplary endothelial cells that may be used according to these assays include bovine aortic endothelial cells (BAEC), which are an example of endothelial cells which line blood vessels and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p>



					<p>indications that stimulate angiogenesis and/or cardiovascularization. Highly preferred are indications that inhibit angiogenesis and/or cardiovascularization. Highly preferred indications include antiangiogenic activity to treat solid tumors, leukemias, and Kaposi's sarcoma, and retinal disorders. Highly preferred indications include neoplasms and cancer, such as, Kaposi's sarcoma, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, lymphangioma, lymphangiosarcoma. Highly preferred indications also include cancers such as, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications also include arterial disease, such as, atherosclerosis, hypertension, coronary artery disease, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, restenosis;</p>
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					<p>venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, and cancer. Highly preferred indications also include trauma such as wounds, burns, and injured tissue (e.g., vascular injury such as, injury resulting from balloon angioplasty, and atherosclerotic lesions), implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. Additional highly preferred indications include stroke, graft rejection, diabetic or other retinopathies, thrombotic and coagulative disorders, vasculitis, lymph angiogenesis, sexual disorders, age-related macular degeneration, and treatment /prevention of endometriosis and related conditions. Additional highly preferred indications include fibromas, heart disease, cardiac arrest, heart valve disease, and vascular disease. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis</p>

228	HTLEP53	632	<p>Activation of transcription through serum response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that</p>	<p>and/or as described below) and immunodeficiencies (e.g., as described below). Additional preferred indications include inflammation and inflammatory disorders (such as acute and chronic inflammatory diseases, e.g., inflammatory bowel disease and Crohn's disease), and pain management.</p> <p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis.</p>
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				<p>may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an</p>
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228	HTLEP53	632	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly</p>	<p>infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal</p>
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				<p>available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
228	HTLEP33	632	<p>Activation of transcription through GATA-3 response element in immune cells (such as mast cells).</p>	<p>This reporter assay measures activation of the GATA-3 signaling pathway in HMC-1 human mast cell line. Activation of GATA-3 in mast cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the GATA3 response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate GATA3 transcription factors and modulate expression of mast cell genes important for immune response development. Exemplary assays for transcription through the GATA3</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred</p>

				<p>response element that may be used or routinely modified to test GATA3-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Flavell et al., Cold Spring Harb Symp Quant Biol 64:563-571 (1999); Rodriguez-Palmero et al., Eur J Immunol 29(12):3914-3924 (1999); Zheng and Flavell, Cell 89(4):587-596 (1997); and Henderson et al., Mol Cell Biol 14(6):4286-4294 (1994), the contents of each of which are herein incorporated by reference in its entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p>	<p>indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
228	HTLEP53	632	Activation of transcription through NFAT response element in immune	<p>This reporter assay measures activation of the NFAT signaling pathway in HMC-1 human mast cell line. Activation of NFAT in mast</p>	<p>Highly preferred indications include allergy, asthma, and rhinitis. Additional preferred indications include infection (e.g., an infectious</p>

			cells (such as mast cells).	<p>cells has been linked to cytokine and chemokine production. Assays for the activation of transcription through the Nuclear Factor of Activated T cells (NFAT) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFAT transcription factors and modulate expression of genes involved in immunomodulatory functions. Exemplary assays for transcription through the NFAT response element that may be used or routinely modified to test NFAT-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); De Boer et al., Int J Biochem Cell Biol 31(10):1221-1236 (1999); Ali et al., J Immunol 165(12):7215-7223 (2000); Hutchinson and McCloskey, J Biol Chem 270(27):16333-16338 (1995), and Turner et al., J Exp Med 188:527-537 (1998), the contents of each of which are herein incorporated by reference in its</p>	<p>disease as described below under "Infectious Disease"), and inflammation and inflammatory disorders. Preferred indications also include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary tract cancers and/or as described below under "Hyperproliferative Disorders"). Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, leukemias, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia,</p>
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229	HTOIY21	633	Activation of Skeletal Muscle Cell ERK Signalling Pathway	<p>entirety. Mast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human mast cells that may be used according to these assays include the HMC-1 cell line, which is an immature human mast cell line established from the peripheral blood of a patient with mast cell leukemia, and exhibits many characteristics of immature mast cells.</p> <p>Kinase assay. Kinase assays, for examplek Elk-1 kinase assays, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature</p>	<p>neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, and Lyme Disease.</p>
				<p>Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders") and disorders of the musculoskeletal system.</p> <p>Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic</p>	

				<p>410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain.</p>
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230	HTPCS72	634	Stimulation of Calcium Flux in pancreatic beta cells.	Assays for measuring calcium flux are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mobilize calcium. For example, the FLPR assay may be used to measure influx of calcium.	<p>Additional highly preferred indications are complications associated with insulin resistance.</p> <p>Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p> <p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Highly preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders"</p>
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				<p>Cells normally have very low concentrations of cytosolic calcium compared to much higher extracellular calcium. Extracellular factors can cause an influx of calcium, leading to activation of calcium responsive signaling pathways and alterations in cell functions. Exemplary assays that may be used or routinely modified to measure calcium flux by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Satin LS, et al., Endocrinology, 136(10):4589-601 (1995); Mogami H, et al., Endocrinology, 136(7):2960-6 (1995); Richardson SB, et al., Biochem J, 288 ( Pt 3):847-51 (1992); and, Meats, JE, et al., Cell Calcium 1989 Nov-Dec;10(8):535-41 (1989), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin,</p>	<p>section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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231	HTPIH83	635	Insulin Secretion	<p>which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p> <p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et. al., Journal of Biomolecular Screening,</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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				<p>4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777</p> <p>Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
232	HTSEW17	636	<p>Stimulation of insulin secretion from pancreatic beta cells.</p>	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to</p>

				<p>diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et. al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
	HTSEW17	636	Activation of transcription through NFKB response element in immune	Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely	Preferred embodiments of the invention include using polypeptides of the invention (or antibodies, agonists, or antagonists thereof) in
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			cells (such as B-cells).	<p>modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFκB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFκB response element that may be used or routinely modified to test NFκB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Gri G, et al., Biol Chem, 273(11):6431-6438 (1998); Pyatt DW, et al., Cell Biol Toxicol 2000;16(1):41-51 (2000); Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. Immune cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary immune cells that may be used according to these assays include the Reh B-cell line.</p>	<p>detection, diagnosis, prevention, and/or treatment of Cancer, Autoimmunity, Allergy and Asthma</p>
HTTB176	637	Stimulation of insulin	Assays for measuring secretion of	A highly preferred indication is	



233			secretion from pancreatic beta cells.	<p>insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells</p>	<p>diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity</p>
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				are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Asfari et al. Endocrinology 1992 130:167.	and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
234	HTBS64	638	Regulation of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and MEed identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol	A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision

				<p>Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
235	HTWKE60	639	<p>Production of VCAM in endothelial cells (such as human umbilical vein endothelial cells (HUVEC))</p>	<p>Assays for measuring expression of VCAM are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate VCAM expression. For example, FMAT may be used to measure the upregulation of cell surface VCAM-1 expression in endothelial cells. Endothelial cells are cells that line</p>	<p>Highly preferred indications include inflammation (acute and chronic), restenosis, atherosclerosis, asthma and allergy. Highly preferred indications include inflammation and inflammatory disorders, immunological disorders, neoplastic disorders (e.g. cancer/tumorigenesis), and cardiovascular disorders (such as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative</p>

			<p>blood vessels, and are involved in functions that include, but are not limited to, angiogenesis, vascular permeability, vascular tone, and immune cell extravasation.</p> <p>Exemplary endothelial cells that may be used according to these assays include human umbilical vein endothelial cells (HUEC), which are available from commercial sources. The expression of VCAM (CD106), a membrane-associated protein, can be upregulated by cytokines or other factors, and contributes to the extravasation of lymphocytes, leucocytes and other immune cells from blood vessels; thus VCAM expression plays a role in promoting immune and inflammatory responses.</p>	<p>Disorders" and/or "Cardiovascular Disorders"). Highly preferred indications include neoplasms and cancers such as, for example, leukemia, lymphoma, melanoma, renal cell carcinoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
236	HTXAJ12	640	<p>Activation of Adipocyte ERK Signaling Pathway</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing)</p>

			<p>antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as</p>
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					described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of
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237	HTXJM03	641	Regulation of Malic Enzyme in hepatocytes	Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin.	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p> <p>the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
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			<p>ME promoter contains two direct repeat (DR1)-like elements. MEp and MED identified as putative PPAR response elements. ME promoter may also responds to AP1 and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994); Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the mouse 3T3-L1 cell line. 3T3-L1 is a mouse preadipocyte cell line (adherent). It is a continuous substrain of 3T3 fibroblasts developed through clonal</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
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238	HTXKF95	642	Activation of Skeletal Muscle Cell ERK Signalling Pathway	isolation. Cells undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation culture conditions.	<p>Kinase assay. Kinase assays, for examplek Elk-1 kinase assays, for ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Rat myoblast cells that may be used according to these assays are publicly available (e.g., through the</p> <p>Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders") and disorders of the musculoskeletal system. Preferred indications include neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease,</p>
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				<p>ATCC). Exemplary rat myoblast cells that may be used according to these assays include L6 cells. L6 is an adherent rat myoblast cell line, isolated from primary cultures of rat thigh muscle, that fuses to form multinucleated myotubes and striated fibers after culture in differentiation media.</p>	<p>stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein.</p>
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239	HTXON32	643	Insulin Secretion	<p>Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion</p>	<p>Additional highly preferred indications include: myopathy, atrophy, congestive heart failure, cachexia, myxomas, fibromas, congenital cardiovascular abnormalities, heart disease, cardiac arrest, heart valve disease, and vascular disease. Highly preferred indications include neoplasms and cancer, such as, rhabdomyoma, rhabdosarcoma, stomach, esophageal, prostate, and urinary cancer. Highly preferred indications also include breast, lung, colon, pancreatic, brain, and liver cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, hyperplasia, metaplasia, and/or dysplasia.</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic</p>
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				<p>(from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Shimizu, H., et al., Endocr J, 47(3):261-9 (2000); Salapatek, A.M., et al., Mol Endocrinol, 13(8):1305-17 (1999); Filipsson, K., et al., Ann N Y Acad Sci, 865:441-4 (1998); Olson, L.K., et al., J Biol Chem, 271(28):16544-52 (1996); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include HIT15 Cells. HIT15 are an adherent epithelial cell line established from Syrian hamster islet cells transformed with SV40. These cells express glucagon, somatostatin, and glucocorticoid receptors. The cells secrete insulin, which is stimulated by glucose and glucagon and suppressed by somatostatin or glucocorticoids. ATTC# CRL-1777 Refs: Lord and Ashcroft. Biochem. J. 219: 547-551; Santerre et al. Proc. Natl. Acad. Sci. USA 78: 4339-4343, 1981.</p>	<p>hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
HUFC130	644	Stimulation of insulin	Assays for measuring secretion of	A highly preferred indication is	

			<p>secretion from pancreatic beta cells.</p>	<p>insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., <i>Am J Physiol</i>, 277(4 Pt 2):R959-66 (1999); Li, M., et al., <i>Endocrinology</i>, 138(9):3735-40 (1997); Kim, K.H., et al., <i>FEBS Lett</i>, 377(2):237-9 (1995); and, Miraglia S et. al., <i>Journal of Biomolecular Screening</i>, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells</p>	<p>diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity</p>
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				are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion. References: Afari et al. Endocrinology 1992 130:167.	and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.
241	HUVEB53	645	Regulation of apoptosis in pancreatic beta cells.	<p>Caspase Apoptosis. Assays for caspase apoptosis are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote caspase protease-mediated apoptosis. Apoptosis in pancreatic beta is associated with induction and progression of diabetes. Exemplary assays for caspase apoptosis that may be used or routinely modified to test caspase apoptosis activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in: Loweth, AC, et al., FEBS Lett, 400(3):285-8 (1997); Saini, KS, et al., Biochem Mol Biol Int, 39(6):1229-36 (1996); Krautheim, A., et al., Br J Pharmacol, 129(4):687-94 (2000); Chandra J, et al., Diabetes, 50 Suppl 1:S44-7 (2001); Suk K, et al., J Immunol, 166(7):4481-9 (2001); Tejedo J, et al., FEBS Lett, 459(2):238-43 (1999); Zhang, S., et al., FEBS Lett,</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision</p>

				<p>455(3):315-20 (1999); Lee et al., FEBS Lett 485(2-3): 122-126 (2000); Nor et al., J Vasc Res 37(3): 209-218 (2000); and Karsan and Harlan, J Atheroscler Thromb 3(2): 75-80 (1996); the contents of each of which are herein incorporated by reference in its entirety. Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include RIN-m. RIN-m is a rat adherent pancreatic beta cell insulinoma cell line derived from a radiation induced transplantable rat islet cell tumor. The cells produce and secrete islet polypeptide hormones, and produce insulin, somatostatin, and possibly glucagon. ATTC: #CRL-2057</p> <p>Chick et al. Proc. Natl. Acad. Sci. 1977 74:628; AF et al. Proc. Natl. Acad. Sci. 1980 77:3519.</p>	<p>impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
242	HWAAD63	646	<p>Regulation of transcription through the FAS promoter element in hepatocytes</p>	<p>Assays for the regulation of transcription through the FAS promoter element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to activate the FAS promoter element in a reporter construct and to regulate transcription of FAS, a key enzyme for lipogenesis. FAS promoter is</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p>

				<p>regulated by many transcription factors including SREBP. Insulin increases FAS gene transcription in livers of diabetic mice. This stimulation of transcription is also somewhat glucose dependent. Exemplary assays that may be used or routinely modified to test for FAS promoter element activity (in hepatocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Xiong, S., et al., Proc Natl Acad Sci U.S.A., 97(8):3948-53 (2000); Roder, K., et al., Eur J Biochem, 260(3):743-51 (1999); Oskouian B, et al., Biochem J, 317 (Pt 1):257-65 (1996); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays, such as H4IIE cells, are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays include rat liver hepatoma cell line(s) inducible with glucocorticoids, insulin, or cAMP derivatives.</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
243	HWADJ89	647	<p>Activation of transcription through serum response element in immune cells (such</p>	<p>Assays for the activation of transcription through the Serum Response Element (SRE) are well-known in the art and may be used or</p>	<p>A preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) TNF alpha production. An alternative preferred</p>



			as T-cells).	<p>routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate the serum response factors and modulate the expression of genes involved in growth. Exemplary assays for transcription through the SRE that may be used or routinely modified to test SRE activity of the polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); and Black et al., Virus Genes 12(2):105-117 (1997), the content of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse T cells that may be used according to these assays include the CTLL cell line, which is an IL-2 dependent suspension culture of T cells with cytotoxic activity.</p>	<p>embodiment of the invention includes a method for stimulating (e.g., increasing) TNF alpha production. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional highly preferred indications include inflammation and inflammatory disorders, and treating joint damage in patients with rheumatoid arthritis. An additional highly preferred indication is sepsis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Additionally, highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, glioma (e.g., malignant glioma), solid tumors, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and</p>
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243	HWADJ89	647	Stimulation of insulin secretion from pancreatic beta cells.	Assays for measuring secretion of insulin are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate insulin secretion. For example, insulin secretion is measured by FMAT using anti-rat insulin antibodies. Insulin secretion from pancreatic beta cells is upregulated by glucose and	<p>urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, cardiac reperfusion injury, and asthma and allergy. An additional preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy),</p>
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				<p>also by certain proteins/peptides, and dysregulation is a key component in diabetes. Exemplary assays that may be used or routinely modified to test for stimulation of insulin secretion (from pancreatic cells) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Ahren, B., et al., Am J Physiol, 277(4 Pt 2):R959-66 (1999); Li, M., et al., Endocrinology, 138(9):3735-40 (1997); Kim, K.H., et al., FEBS Lett, 377(2):237-9 (1995); and, Miraglia S et al., Journal of Biomolecular Screening, 4:193-204 (1999), the contents of each of which is herein incorporated by reference in its entirety.</p> <p>Pancreatic cells that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary pancreatic cells that may be used according to these assays include rat INS-1 cells. INS-1 cells are a semi-adherent cell line established from cells isolated from an X-ray induced rat transplantable insulinoma. These cells retain characteristics typical of native pancreatic beta cells including glucose inducible insulin secretion.</p> <p>References: Asfari et al. Endocrinology 1992 130:167.</p>	<p>blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
244	HWBCP79	648	Activation of Adipocyte ERK	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for</p>	<p>A highly preferred embodiment of the invention includes a method</p>

			<p>ERK signal transduction that regulate cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of</p>	<p>for stimulating adipocyte proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune</p>
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				<p>3T3 fibroblast cells developed through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.</p>	<p>disorders (e.g., as described below under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease").</p> <p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired</p>
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					<p>wound healing, infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-</p>
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244	HWBCP79	648	Production of IL-10 and activation of T-cells.	Assays for production of IL-10 and activation of T-cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to stimulate or inhibit production of IL-10 and/or activation of T-cells. Exemplary assays that may be used or routinely modified to assess the ability of polypeptides and antibodies of the invention (including agonists or antagonists of the invention) to modulate IL-10 production and/or T-cell proliferation include, for example, assays such as disclosed and/or cited in: Robinson, DS, et al., "Th-2 cytokines in allergic disease" Br Med Bull; 56 (4): 956-968 (2000), and Cohn, et al., "T-helper type 2 cell-directed therapy for asthma" Pharmacology & Therapeutics; 88: 187-196 (2000); the contents of each of which are herein incorporated by reference in their entirety. Exemplary cells that may be used according to these assays include Th2 cells. IL10 secreted from Th2 cells may be measured as a marker of Th2 cell activation. Th2 cells are a class of T cells that secrete IL4, IL10, IL13, IL5 and IL6. Factors that induce	neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.  Highly preferred indications include allergy and asthma. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response.
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246	HWBFX31	650	Regulation of Malic Enzyme in adipocytes	<p>differentiation and activation of Th2 cells play a major role in the initiation and pathogenesis of allergy and asthma. Primary T helper 2 cells are generated via in vitro culture under Th2 polarizing conditions using peripheral blood lymphocytes isolated from cord blood.</p> <p>Assays for the regulation of transcription of Malic Enzyme are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate transcription of Malic Enzyme, a key enzyme in lipogenesis. Malic enzyme is involved in lipogenesis and its expression is stimulated by insulin. ME promoter contains two direct repeat (DR1)-like elements MEp and ME<sub>d</sub> identified as putative PPAR response elements. ME promoter may also respond to API and other transcription factors. Exemplary assays that may be used or routinely modified to test for regulation of transcription of Malic Enzyme (in adipocytes) by polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in: Streeper, R.S., et al., Mol Endocrinol, 12(11):1778-91 (1998); Garcia-Jimenez, C., et al., Mol Endocrinol, 8(10):1361-9 (1994);</p>	<p>A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy</p>
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247	HWHGZ51	651		<p>Barroso, I., et al., J Biol Chem, 274(25):17997-8004 (1999); Ijpenberg, A., et al., J Biol Chem, 272(32):20108-20117 (1997); Berger, et al., Gene 66:1-10 (1988); and, Cullen, B., et al., Methods in Enzymol. 216:362-368 (1992), the contents of each of which is herein incorporated by reference in its entirety. Hepatocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary hepatocytes that may be used according to these assays includes the H4IIE rat liver hepatoma cell line.</p>	<p>and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance.</p>
			<p>Activation of transcription through GAS response element in immune cells (such as T-cells).</p>	<p>Assays for the activation of transcription through the Gamma Interferon Activation Site (GAS) response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate STAT transcription factors and modulate gene expression involved in a wide variety of cell functions. Exemplary assays for transcription through the GAS response element that may be used or routinely modified to test GAS-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include</p>	<p>Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma (e.g., T cell lymphoma, Burkitt's lymphoma, non-Hodgkins lymphoma, Hodgkin's disease), melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications</p>

				<p>assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Matikainen et al., Blood 93(6):1980-1991 (1999); and Henttinen et al., J Immunol 155(10):4582-4587 (1995), the contents of each of which are herein incorporated by reference in its entirety. Exemplary mouse T cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary T cells that may be used according to these assays include the CTLL cell line, which is a suspension culture of IL-2 dependent cytotoxic T cells.</p>	<p>include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response. Additional preferred indications include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or an infectious disease as described below under "Infectious Disease"). An additional preferred indication is idiopathic pulmonary fibrosis. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus,</p>
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247	HWHGZ51	651	Production of MCP-1	<p>MCP-1 FMAT. Assays for immunomodulatory proteins that are produced by a large variety of cells and act to induce chemotaxis and activation of monocytes and T cells are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, induce chemotaxis, and modulate immune cell activation. Exemplary assays that test for immunomodulatory proteins evaluate the production of cell surface markers, such as monocyte chemoattractant protein (MCP), and the activation of monocytes and T cells. Such assays that may be used or routinely modified to test immunomodulatory and differentiation activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204(1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Sathaporn and Eremin, J R Coll Surg Ednb 45(1):9-19 (2001); and Verhasselt et al., J Immunol 158:2919-2925 (1997), the contents</p>	<p>endocarditis, meningitis, Lyme Disease, and asthma and allergy.</p> <p>A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) MCP-1 production. An alternative highly preferred embodiment of the invention includes a method for inhibiting (e.g., reducing) MCP-1 production. A highly preferred indication is infection (e.g., an infectious disease as described below under "Infectious Disease").</p> <p>Additional highly preferred indications include inflammation and inflammatory disorders. Preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune</p>
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					<p>of each of which are herein incorporated by reference in its entirety. Human dendritic cells that may be used according to these assays may be isolated using techniques disclosed herein or otherwise known in the art. Human dendritic cells are antigen presenting cells in suspension culture, which, when activated by antigen and/or cytokines, initiate and upregulate T cell proliferation and functional activities.</p>	<p>reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis (bacterial and viral), Lyme Disease, asthma, and allergy Preferred indications also include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia.</p>
247	HWHGZ51	651	Activation of transcription through NFKB response element in immune cells (such as EOL1 cells).		<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of</p>	<p>Highly preferred indications include asthma, allergy, hypersensitivity reactions, and inflammation. Preferred indications include infection (e.g., an infectious disease as described below under "Infectious Disease"), immunological disorders, inflammation and inflammatory disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"). Preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and</p>

				<p>the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. For example, a reporter assay (which measures increases in transcription inducible from a NFkB responsive element in EOL-1 cells) may link the NFkB element to a reporter gene and binds to the NFkB transcription factor, which is upregulated by cytokines and other factors. Exemplary immune cells that may be used according to these assays include eosinophils such as the human EOL-1 cell line of eosinophils.</p> <p>Eosinophils are a type of immune cell important in the allergic responses; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Eol-1 is a human eosinophil cell line.</p>	immunodeficiencies (e.g., as described below).
248	HW/TBK81	652	Activation of Adipocyte ERK Signaling Pathway	<p>Kinase assay. Kinase assays, for example an Elk-1 kinase assay, for ERK signal transduction that regulate</p> <p>A highly preferred embodiment of the invention includes a method for stimulating adipocyte</p>	

			<p>cell proliferation or differentiation are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to promote or inhibit cell proliferation, activation, and differentiation. Exemplary assays for ERK kinase activity that may be used or routinely modified to test ERK kinase-induced activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Forrer et al., Biol Chem 379(8-9):1101-1110 (1998); Le Marchand-Brustel Y, Exp Clin Endocrinol Diabetes 107(2):126-132 (1999); Kyriakis JM, Biochem Soc Symp 64:29-48 (1999); Chang and Karin, Nature 410(6824):37-40 (2001); and Cobb MH, Prog Biophys Mol Biol 71(3-4):479-500 (1999); the contents of each of which are herein incorporated by reference in its entirety. Mouse adipocyte cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed</p>	<p>proliferation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte proliferation. A highly preferred embodiment of the invention includes a method for stimulating adipocyte differentiation. An alternative highly preferred embodiment of the invention includes a method for inhibiting adipocyte differentiation. A highly preferred embodiment of the invention includes a method for stimulating (e.g., increasing) adipocyte activation. An alternative highly preferred embodiment of the invention includes a method for inhibiting the activation of (e.g., decreasing) and/or inactivating adipocytes. Highly preferred indications include endocrine disorders (e.g., as described below under "Endocrine Disorders"). Highly preferred indications also include neoplastic diseases (e.g., lipomas, liposarcomas, and/or as described below under "Hyperproliferative Disorders"). Preferred indications include blood disorders (e.g., hypertension, congestive heart failure, blood vessel blockage, heart disease, stroke, impotence and/or as described below under "Immune Activity", "Cardiovascular Disorders", and/or "Blood-Related Disorders"), immune disorders (e.g., as described below</p>
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				through clonal isolation and undergo a pre-adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art.	under "Immune Activity"), neural disorders (e.g., as described below under "Neural Activity and Neurological Diseases"), and infection (e.g., as described below under "Infectious Disease"). A highly preferred indication is diabetes mellitus. An additional highly preferred indication is a complication associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infection (e.g.,
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				<p>infectious diseases and disorders as described in the "Infectious Diseases" section below (particularly of the urinary tract and skin). An additional highly preferred indication is obesity and/or complications associated with obesity. Additional highly preferred indications include weight loss or alternatively, weight gain. Additional highly preferred indications are complications associated with insulin resistance. Additional highly preferred indications are disorders of the musculoskeletal systems including myopathies, muscular dystrophy, and/or as described herein. Additional highly preferred indications include, hypertension, coronary artery disease, dyslipidemia, gallstones, osteoarthritis, degenerative arthritis, eating disorders, fibrosis, cachexia, and kidney diseases or disorders. Preferred indications include neoplasms and cancer, such as, lymphoma, leukemia and breast, colon, and kidney cancer. Additional preferred indications include melanoma, prostate, lung, pancreatic, esophageal, stomach, brain, liver, and urinary cancer. Highly preferred indications include lipomas and liposarcomas. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for</p>
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248	HW/TBK81	652	<p>Activation of transcription through NFKB response element in immune cells (such as the Jurkat human T cell line).</p>	<p>Assays for the activation of transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Arambourau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. T cells that may be used according to these assays are publicly available (e.g., through the ATCC). T cells that may be used according to these assays are publicly</p>	<p>example, hyperplasia, metaplasia, and/or dysplasia.</p> <p>Highly preferred indications include inflammation and inflammatory disorders. Highly preferred indications include immunological and hematopoietic disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders").</p> <p>Highly preferred indications include neoplasms and cancers, such as, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia,</p>
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249	HAGAI85	653		<p>available (e.g., through the ATCC). Exemplary human T cells that may be used according to these assays include the JURKAT cell line, which is a suspension culture of leukemia cells that produce IL-2 when stimulated.</p>	<p>and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>
			Production of GM-CSF	<p>GM-CSF FMAT. GM-CSF is expressed by activated T cells, macrophages, endothelial cells, and fibroblasts. GM-CSF regulates differentiation and proliferation of granulocytes- macrophage progenitors and enhances antimicrobial activity in neutrophils, monocytes and macrophage. Additionally, GM-CSF plays an important role in the differentiation of dendritic cells and monocytes, and increases antigen presentation. GM-CSF is considered to be a proinflammatory cytokine. Assays for immunomodulatory proteins that promote the production of GM-CSF are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating the production of GM-CSF. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of GM-CSF. Highly preferred indications include inflammation and inflammatory disorders. An additional highly preferred indication is infection (e.g., as described below under "Infectious Disease". Highly preferred indications include blood disorders (e.g., neutropenia (and the prevention of neutropenia (e.g., in HIV infected patients), and/or as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred</p>

				<p>agonists or antagonists of the invention) to mediate immunomodulation and modulate the growth and differentiation of leukocytes. Exemplary assays that test for immunomodulatory proteins evaluate the production of cytokines, such as GM-CSF, and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); and Ye et al., J Leukoc Biol (58(2):225-233, the contents of each of which are herein incorporated by reference in its entirety. Natural killer cells that may be used according to these assays are publicly available (e.g., through the ATCC) or may be isolated using techniques disclosed herein or otherwise known in the art. Natural killer (NK) cells are large granular lymphocytes that have cytotoxic activity but do not bind antigen. NK cells show antibody-independent killing of tumor cells and also recognize antibody bound on target cells, via NK Fc receptors, leading to cell-mediated cytotoxicity.</p>	<p>indications also include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below) and immunodeficiencies (e.g., as described below). Additional highly preferred indications include asthma. Highly preferred indications include neoplastic diseases (e.g., leukemia (e.g., acute lymphoblastic leukemia, and acute myelogenous leukemia), lymphoma (e.g., non-Hodgkin's lymphoma and Hodgkin's disease), and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Highly preferred indications include: suppression of immune reactions to transplanted organs and tissues (e.g., bone marrow transplant); accelerating myeloid recovery; and mobilizing hematopoietic progenitor cells. Preferred indications include boosting a T cell-mediated immune response, and alternatively, suppressing a T cell-mediated</p>
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					<p>immune response. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, and allergy.</p>
249	HAGAI85	653	Production of IFNgamma using Natural Killer cells	<p>IFNgamma FMAT. IFNg plays a central role in the immune system and is considered to be a proinflammatory cytokine. IFNg promotes TH1 and inhibits TH2; promotes IgG2a and inhibits IgE; induces macrophage activation; and increases MHC expression. Assays for immunomodulatory proteins produced by T cells and NK cells that regulate a variety of inflammatory activities and inhibit TH2 helper cell functions are well known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to mediate immunomodulation, regulate inflammatory activities, modulate TH2 helper cell function, and/or mediate humoral or cell-mediated immunity. Exemplary assays that</p>	<p>A highly preferred embodiment of the invention includes a method for stimulating the production of IFNg. An alternative highly preferred embodiment of the invention includes a method for inhibiting the production of IFNg. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", "Hyperproliferative Disorders" (e.g. cancer/tumorigenesis) and/or "Cardiovascular Disorders"), and infection (e.g., viral infections, tuberculosis, infections associated with chronic granulomatous disease and malignant osteoporosis, and/or as described below under "Infectious Disease"). Highly preferred indications include autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described</p>

			<p>test for immunomodulatory proteins evaluate the production of cytokines, such as Interferon gamma (IFNg), and the activation of T cells. Such assays that may be used or routinely modified to test immunomodulatory activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include the assays disclosed in Miraglia et al., J Biomolecular Screening 4:193-204 (1999); Rowland et al., "Lymphocytes: a practical approach" Chapter 6:138-160 (2000); Gonzalez et al., J Clin Lab Anal 8(5):225-233 (1995); Billiau et al., Ann NY Acad Sci 856:22-32 (1998); Boehm et al., Annu Rev Immunol 15:749-795 (1997), and Rheumatology (Oxford) 38(3):214-20 (1999), the contents of each of which are herein incorporated by reference in its entirety. Natural Killer (NK) cells that may be used according to these assays are publicly available (e.g., through the ATCC) or may be isolated using techniques disclosed herein or otherwise known in the art. Natural killer (NK) cells are large granular lymphocytes that have cytotoxic activity but do bind antigen. NK cells show antibody-independent killing of tumor cells and also recognize antibody bound on target cells, via NK Fc receptors, leading to cell-mediated cytotoxicity.</p>	<p>below), immunodeficiency (e.g., as described below), boosting a T cell-mediated immune response, and suppressing a T cell-mediated immune response, boosting antibody-dependent immune responses, suppressing antibody-dependent immune responses, boosting innate immunity and immune responses, and suppressing innate immunity and immune responses. Additional highly preferred indications include inflammation and inflammatory disorders. Additional preferred indications include idiopathic pulmonary fibrosis. Highly preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, melanoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, leukemia, lymphoma, melanoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications include anemia, pancytopenia, leukopenia, thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL),</p>
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250	HOFOC33	654	Proliferation of pre-adipose cells (such as 3T3-L1 cells)	Assays for the regulation (i.e. increases or decreases) of viability and proliferation of cells in vitro are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate viability and proliferation of pre-adipose cells and cell lines. For example, the CellTiter-Glo™ Luminescent Cell Viability Assay (Promega Corp., Madison, WI, USA) can be used to measure the number of viable cells in culture based on quantitation of the ATP present which signals the presence of metabolically active cells. 3T3-L1 is a mouse preadipocyte cell line. It is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation. . See Green H and Meuth M., Cell 3: 127-133 (1974), which is herein incorporated by reference in its entirety.	plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, suppression of immune reactions to transplanted organs and tissues, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, asthma and allergy.
	HOFOC33	654	Activation of	Assays for the activation of	Highly preferred indications

250	transcription through NFKB response element in immune cells (such as natural killer cells).	transcription through the NFKB response element are well-known in the art and may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to regulate NFKB transcription factors and modulate expression of immunomodulatory genes. Exemplary assays for transcription through the NFKB response element that may be used or routinely modified to test NFKB-response element activity of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) include assays disclosed in Berger et al., Gene 66:1-10 (1998); Cullen and Malm, Methods in Enzymol 216:362-368 (1992); Henthorn et al., Proc Natl Acad Sci USA 85:6342-6346 (1988); Valle Blazquez et al, Immunology 90(3):455-460 (1997); Aramburau et al., J Exp Med 82(3):801-810 (1995); and Fraser et al., 29(3):838-844 (1999), the contents of each of which are herein incorporated by reference in its entirety. NK cells that may be used according to these assays are publicly available (e.g., through the ATCC). Exemplary human NK cells that may be used according to these assays include the NK1 cell line, which is a human natural killer cell line established from the peripheral	include inflammation and inflammatory disorders. Highly preferred indications include blood disorders (e.g., as described below under "Immune Activity", "Blood-Related Disorders", and/or "Cardiovascular Disorders"). Highly preferred indications include autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and/or as described below), and immunodeficiencies (e.g., as described below). An additional highly preferred indication is infection (e.g., AIDS, and/or an infectious disease as described below under "Infectious Disease"). Highly preferred indications include neoplastic diseases (e.g., melanoma, leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include neoplasms and cancers, such as, for example, melanoma, renal cell carcinoma, leukemia, lymphoma, and prostate, breast, lung, colon, pancreatic, esophageal, stomach, brain, liver and urinary cancer. Other preferred indications include benign dysproliferative disorders and pre-neoplastic conditions, such as, for example, hyperplasia, metaplasia, and/or dysplasia. Preferred indications also include anemia, pancytopenia, leukopenia,
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251	HSDEZ20	655	Inhibition of adipocyte ERK signaling pathway.	<p>blood of a patient with large granular lymphocytic leukemia. This IL-2 dependent suspension culture cell line has a morphology resembling that of activated NK cells.</p> <p>Kinase assay: measures the phosphorylation of Elk-1, an indication of activation of extracellular signal regulated kinase (ERK). ERK pathway regulates cell growth, proliferation and differentiation. Cells were pretreated with SID supernatants for 15-18 hours, and then 100 nM of insulin was added to stimulate ERK kinase. Phosphorylation of Elk-1 was measured after a 20 minute incubation. Pre-adipocytes that may be used according to these assays are publicly available (e.g., through the ATCC) and/or may be routinely generated. Exemplary mouse adipocyte cells that may be used according to these assays include 3T3-L1 cells. 3T3-L1 is an adherent mouse preadipocyte cell line that is a continuous substrain of 3T3 fibroblast cells developed through clonal isolation and undergo a pre-</p>	<p>thrombocytopenia, Hodgkin's disease, acute lymphocytic anemia (ALL), plasmacytomas, multiple myeloma, Burkitt's lymphoma, arthritis, AIDS, granulomatous disease, inflammatory bowel disease, sepsis, neutropenia, neutrophilia, psoriasis, hemophilia, hypercoagulation, diabetes mellitus, endocarditis, meningitis, Lyme Disease, suppression of immune reactions to transplanted organs, asthma and allergy.</p>
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251	HSDEZZ0	655	Activation of JNK Signaling Pathway in immune cells (such as eosinophils).	adipocyte to adipose-like conversion under appropriate differentiation conditions known in the art. Cells were differentiated to an adipose-like state before being used in the screen. See Green et al., Cell 3: 127-133 (1974), the contents of which are herein incorporated by reference in its entirety.	Highly preferred indications include asthma, allergy, hypersensitivity reactions, inflammation, and inflammatory disorders. Additional highly preferred indications include immune and hematopoietic disorders (e.g., as described below under "Immune Activity", and "Blood-Related Disorders"), autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, multiple sclerosis and/or as described below), immunodeficiencies (e.g., as described below). Highly preferred indications also include boosting or inhibiting immune cell proliferation. Preferred indications include neoplastic diseases (e.g., leukemia, lymphoma, and/or as described below under "Hyperproliferative Disorders"). Highly preferred indications include boosting an eosinophil-mediated immune response, and suppressing an eosinophil-mediated immune response.
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				<p>entirety. Exemplary cells that may be used according to these assays include eosinophils. Eosinophils are important in the late stage of allergic reactions; they are recruited to tissues and mediate the inflammatory response of late stage allergic reaction. Moreover, exemplary assays that may be used or routinely modified to assess the ability of polypeptides of the invention (including antibodies and agonists or antagonists of the invention) to modulate signal transduction, cell proliferation, activation, or apoptosis in eosinophils include assays disclosed and/or cited in: Zhang JP, et al., "Role of caspases in dexamethasone-induced apoptosis and activation of c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase in human eosinophils" Clin Exp Immunol; Oct;122(1):20-7 (2000); Hebestreit H, et al., "Disruption of fas receptor signaling by nitric oxide in eosinophils" J Exp Med; Feb 2;187(3):415-25 (1998); J Allergy Clin Immunol 1999 Sep;104(3 Pt 1):565-74; and, Sousa AR, et al., "In vivo resistance to corticosteroids in bronchial asthma is associated with enhanced phosphorylation of JUN N-terminal kinase and failure of prednisolone to inhibit JUN N-terminal kinase phosphorylation" J Allergy Clin Immunol; Sep;104(3 Pt 1):565-74</p>
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					(1999), the contents of each of which are herein incorporated by reference in its entirety.	
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**Table 1E:** Polynucleotides encoding polypeptides of the present invention can be used in assays to test for one or more biological activities. One such biological activity which may be tested includes the ability of polynucleotides and polypeptides of the invention to stimulate up-regulation or down-regulation of expression of particular genes and proteins. Hence, if polynucleotides and polypeptides of the present invention exhibit activity in altering particular gene and protein expression patterns, it is likely that these polynucleotides and polypeptides of the present invention may be involved in, or capable of effecting changes in, diseases associated with the altered gene and protein expression profiles. Hence, polynucleotides, polypeptides, or antibodies of the present invention could be used to treat said associated diseases.

TaqMan® assays may be performed to assess the ability of polynucleotides (and polypeptides they encode) to alter the expression pattern of particular "target" genes. TaqMan® reactions are performed to evaluate the ability of a test agent to induce or repress expression of specific genes in different cell types. TaqMan® gene expression quantification assays ("TaqMan® assays") are well known to, and routinely performed by, those of ordinary skill in the art. TaqMan® assays are performed in a two step reverse transcription / polymerase chain reaction (RT-PCR). In the first (RT) step, cDNA is reverse transcribed from total RNA samples using random hexamer primers. In the second (PCR) step, PCR products are synthesized from the cDNA using gene specific primers.

To quantify gene expression the Taqman® PCR reaction exploits the 5' nuclease activity of AmpliTaq Gold® DNA Polymerase to cleave a Taqman® probe (distinct from the primers) during PCR. The Taqman® probe contains a reporter dye at the 5'-end of the probe and a quencher dye at the 3' end of the probe. When the probe is intact, the proximity of the reporter dye to the quencher dye results in suppression of the reporter fluorescence. During PCR, if the target of interest is present, the probe specifically anneals between the forward and reverse primer sites. AmpliTaq Fold DNA Polymerase then cleaves the probe between the reporter and quencher when the probe hybridizes to the target, resulting in increased fluorescence of the reporter (see Figure 2). Accumulation of PCR products is detected directly by monitoring the increase in fluorescence of the reporter dye.

After the probe fragments are displaced from the target, polymerization of the strand continues. The 3'-end of the probe is blocked to prevent extension of the probe during PCR. This process occurs in every cycle and does not interfere with the exponential accumulation of product. The increase in fluorescence signal is detected only if the target sequence is complementary to the probe and is amplified during PCR. Because of these requirements, any nonspecific amplification is not detected.

For test sample preparation, vector controls or constructs containing the coding sequence for the gene of interest are transfected into cells, such as for example 293T cells, and supernatants

collected after 48 hours. For cell treatment and RNA isolation, multiple primary human cells or human cell lines are used; such cells may include but are not limited to, Normal Human Dermal Fibroblasts, Aortic Smooth Muscle, Human Umbilical Vein Endothelial Cells, HepG2, Daudi, Jurkat, U937, Caco, and THP-1 cell lines. Cells are plated in growth media and growth is arrested  
5 by culturing without media change for 3 days, or by switching cells to low serum media and incubating overnight. Cells are treated for 1, 6, or 24 hours with either vector control supernatant or sample supernatant (or purified/partially purified protein preparations in buffer). Total RNA is isolated; for example, by using Trizol extraction or by using the Ambion RNAqueous(TM)-4PCR RNA isolation system. Expression levels of multiple genes are analyzed using TAQMAN, and  
10 expression in the test sample is compared to control vector samples to identify genes induced or repressed. Each of the above described techniques are well known to, and routinely performed by, those of ordinary skill in the art.

Table 1E indicates particular disease classes and preferred indications for which polynucleotides, polypeptides, or antibodies of the present invention may be used in detecting,  
15 diagnosing, preventing, treating and/or ameliorating said diseases and disorders based on "target" gene expression patterns which may be up- or down-regulated by polynucleotides (and the encoded polypeptides) corresponding to each indicated cDNA Clone ID (shown in Table 1E, Column 2).

Thus, in preferred embodiments, the present invention encompasses a method of  
20 detecting, diagnosing, preventing, treating, and/or ameliorating a disease or disorder listed in the "Disease Class" and/or "Preferred Indication" columns of Table 1E; comprising administering to a patient in which such detection, diagnosis, prevention, or treatment is desired a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof) in an amount effective to detect, diagnose, prevent, treat, or ameliorate the disease or disorder. The first and second columns of  
25 Table 1D show the "Gene No." and "cDNA Clone ID No.", respectively, indicating certain nucleic acids and proteins (or antibodies against the same) of the invention (including polynucleotide, polypeptide, and antibody fragments or variants thereof) that may be used in detecting, diagnosing, preventing, treating, or ameliorating the disease(s) or disorder(s) indicated in column 6 and as indicated in the corresponding row in the "Disease Class" or "Preferred Indication" Columns of  
30 Table 1E.

In another embodiment, the present invention also encompasses methods of detecting, diagnosing, preventing, treating, or ameliorating a disease or disorder listed in the "Disease Class" or "Preferred Indication" Columns of Table 1E; comprising administering to a patient  
35 combinations of the proteins, nucleic acids, or antibodies of the invention (or fragments or variants thereof), sharing similar indications as shown in the corresponding rows in the "Disease Class" or "Preferred Indication" Columns of Table 1E.

The "Disease Class" Column of Table 1E provides a categorized descriptive heading for diseases, disorders, and/or conditions (more fully described below) that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

5           The "Preferred Indication" Column of Table 1E describes diseases, disorders, and/or conditions that may be detected, diagnosed, prevented, treated, or ameliorated by a protein, nucleic acid, or antibody of the invention (or fragment or variant thereof).

10           The "Cell Line" and "Exemplary Targets" Columns of Table 1E indicate particular cell lines and target genes, respectively, which may show altered gene expression patterns (i.e., up- or down-regulation of the indicated target gene) in Taqman assays, performed as described above, utilizing polynucleotides of the cDNA Clone ID shown in the corresponding row. Alteration of expression patterns of the indicated "Exemplary Target" genes is correlated with a particular "Disease Class" and/or "Preferred Indication" as shown in the corresponding row under the respective column headings.

15           The "Exemplary Accessions" Column indicates GenBank Accessions (available online through the National Center for Biotechnology Information (NCBI) at <http://www.ncbi.nlm.nih.gov/>) which correspond to the "Exemplary Targets" shown in the adjacent row.

20           The recitation of "Cancer" in the "Disease Class" Column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof) may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate neoplastic diseases and/or disorders (e.g., leukemias, cancers, etc., as described below under "Hyperproliferative Disorders").

25           The recitation of "Immune" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, prevent, treat, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), blood disorders (e.g., as described below under "Immune Activity" "Cardiovascular Disorders" and/or "Blood-Related Disorders"), and infections (e.g., as described below under "Infectious Disease").

30           The recitation of "Angiogenesis" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diseases and/or disorders relating to neoplastic diseases (e.g., as described below under "Hyperproliferative Disorders"), diseases and/or disorders of the cardiovascular system (e.g., as described below under "Cardiovascular Disorders"), diseases and/or disorders involving cellular and genetic abnormalities (e.g., as described below under "Diseases at the Cellular Level"),

diseases and/or disorders involving angiogenesis (e.g., as described below under "Anti-Angiogenesis Activity"), to promote or inhibit cell or tissue regeneration (e.g., as described below under "Regeneration"), or to promote wound healing (e.g., as described below under "Wound Healing and Epithelial Cell Proliferation").

5           The recitation of "Diabetes" in the "Disease Class" column indicates that the corresponding nucleic acid and protein, or antibody against the same, of the invention (or fragment or variant thereof), may be used for example, to detect, diagnose, treat, prevent, and/or ameliorate diabetes (including diabetes mellitus types I and II), as well as diseases and/or disorders associated with, or consequential to, diabetes (e.g. as described below under "Endocrine Disorders," "Renal  
10 Disorders," and "Gastrointestinal Disorders").

Table 1E

Gene No.	cDNA Clone ID	Disease Class	Preferred Indications	Cell Line	Exemplary Targets	Exemplary Accessions
105	HJACG02	Diabetes	A highly preferred indication is diabetes. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases.	Adipocytes (4D)-09/01/01	CAP PEPCK1	gb AF136380 AF136380 gb L05144 HUMPHOCAR
105	HJACG02	Diabetes	A highly preferred indication is diabetes. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases.	Adipocytes-3/12/01	CAP Hexokinase II	gb AF136380 AF136380 gb Z46354 HSHKEX1



			<p>diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases.</p>	AOSMC	IRSI PPARg	gb X90563 HSPP ARGAM
105	HJACG02	Diabetes	<p>A highly preferred indication is diabetes. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection</p>			

			(e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases.(AOSMC cells are human aortic smooth muscle cells).			
105	HJACG02	Diabetes	A highly preferred indication is diabetes. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases.	Liver	Glucose6 phosphatase	gb U91844 CFU9 1844
105	HJACG02	Immune	Highly preferred indications include immunological disorders such	Adipocytes-	ICAM	gb X06990 HSIC

105			as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving adipocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving adipocytes).	3/12/01	IL6 Rag1	AM1 gb X04403 HS26 KDAR gb M29474 HUM RAG1
105	HJACG02	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving muscle tissues and the cardiovascular system (e.g. heart, lungs, circulatory system)). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving muscle tissue or the cardiovascular system). (AOSMC cells are human aortic smooth muscle cells).	AOSMC	CD30 CD40 IL1B IL5 TNF VCAM	gb A300189 HS A30018 gb X02532 HSIL 1BR gb X12705 HSB CDFIA gb A270944 HS A27094 gb A30922 A309 22
105	HJACG02	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the cells of the gastrointestinal tract). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the gastrointestinal tract). (The Caco-2 cell line is a human colorectal adenocarcinoma cell line available through the ATCC as cell line number HTB-37).	Caco-2	Rag1	gb M29474 HUM RAG1
105	HJACG02	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the B-cells). Highly preferred embodiments of the invention include methods of preventing,	Daudi	ICAM Rag1 VCAM	gb X06990 HSIC AM1 gb M29474 HUM RAG1 gb A30922 A309

				detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving B-cells). (The Daudi cell line is a human B lymphoblast cell line available through the ATCC as cell line number CCL-213).		22	
105	HJACG02	Immune		Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving epithelial cells or the renal system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving epithelial cells or the renal system). (The 293 cell line is a human embryonal kidney epithelial cell line available through the ATCC as cell line number CRL-1573).	HEK293	c-maf	gb AF055377 AF055377
105	HJACG02	Immune		Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving endothelial cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving endothelial cells). (HUVEC cells are human umbilical vein endothelial cells).	HUVEC	ICAM	gb X06990 HSICAM1
105	HJACG02	Immune		Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The Jurkat cell line is a human T lymphocyte cell line available through the ATCC as cell line	Jurkat	Rag2 TNF	gb AY011962 AY011962 gb AJ270944 HSA27094

105	HJACG02	Immune	number TIB-152). Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the skin). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving the skin). (NHDF cells are normal human dermal fibroblasts).	NHDF	Rag1	gb M29474 HUM RAG1
105	HJACG02	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The U937 cell line is a human monocyte cell line available through the ATCC as cell line number CRL-1593.2).	U937	GATA1 IL5 TNF	gb X17254 HSER YF1 gb X12705 HSB CDFIA gb AJ270944 HS A27094
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving muscle tissues and the cardiovascular system (e.g. heart, lungs, circulatory system)). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving muscle tissue or the cardiovascular system). (AOSMC cells are human aortic smooth muscle cells).	AOSMC	VCAM	gb A30922 A309 22
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving muscle tissues and the cardiovascular system). (AOSMC cells are human aortic smooth muscle cells).	Daudi	CD40	gb AJ300189 HS A30018

			to, immune disorders involving the B-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving B-cells). (The Daudi cell line is a human B lymphoblast cell line available through the ATCC as cell line number CCL-213).			
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving endothelial cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving endothelial cells). (HUVEC cells are human umbilical vein endothelial cells).	HUVEC	ICAM Rag1	gb X06990 HSIC AM1 gb M29474 HUM RAG1
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving cells of the hepatic system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the hepatic system).	Liver	CD28	gb AF222342 AF 222342
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the skin). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving the skin). (NHDF cells are normal human dermal fibroblasts).	NHDF	CXCR3 GATA1 IL6 VCAM	gb Z79783 HSCK RL2 gb X17254 HSER YF1 gb X04403 HS26 KDAR gb A30922 A309 22
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the skin). (NHDF cells are normal human dermal fibroblasts).	THP1	CIS3	gb AB006967 AB

			as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The THP1 cell line is a human monocyte cell line available through the ATCC as cell line number TIB-202).			006967
110	HKACD58	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The U937 cell line is a human monocyte cell line available through the ATCC as cell line number CRL-1593.2).	U937	CD69 TNF	gb Z22576 HSCD 69GNA gb AJ270944 HS A27094
202	HSDSB09	Diabetes	A highly preferred indication is diabetes. Additional highly preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy	AOSMC	GAPDH	

202	HSDSB09	Immune	and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases. (AOSMC cells are human aortic smooth muscle cells).	AOSMC	CCR3 CCR4 CD25 CD30 CD40 CTLA4 IL5 Rag1 VCAM	gb AB023887 AB 023887 gb AB023888 AB 023888 gb X03137 HSIL 2RG7  gb AJ300189 HS A30018 gb AF316875 AF 316875 gb X12705 HSB CDFIA gb M29474 HUM RAG1 gb A30922 A309 22
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving muscle tissues and the cardiovascular system (e.g. heart, lungs, circulatory system)). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving muscle tissue or the cardiovascular system). (AOSMC cells are human aortic smooth muscle cells).	Caco-2	c-maf GATA3 ICAM Rag1	gb AF055377 AF 055377 gb X55037 HSG ATA3 gb X06990 HSIC AM1 gb M29474 HUM



202	HSDSB09	Immune	including, but not limited to, immune disorders involving cells of the gastrointestinal tract). (The Caco-2 cell line is a human colorectal adenocarcinoma cell line available through the ATCC as cell line number HTB-37).	Daudi	TNF	gb AJ270944 HS A27094	RAG1
			Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the B-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving B-cells). (The Daudi cell line is a human B lymphoblast cell line available through the ATCC as cell line number CCL-213).				
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The H9 cell line is a human T lymphocyte cell line available through the ATCC as cell line number HTB-176).	H9	CIS3 Rag1	gb AB006967 AB 006967 gb M29474 HUM RAG1	
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving epithelial cells or the renal system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving epithelial cells or the renal system). (The 293 cell line is a human embryonal kidney epithelial cell line available through the ATCC as cell line number CRL-	HEK293	CCR3 CCR4 CD25 CD30 CD40 CTLA4 GATA3 Rag1 TNF VCAM	gb AB023887 AB 023887 gb AB023888 AB 023888 gb X03137 HSIL 2RG7  gb AJ300189 HS A30018 gb AF316875 AF	

202	HSDSB09	Immune	1573).			316875 gb X55037 HSG ATA3 gb M29474 HUM RAG1 gb AJ270944 HS A27094 gb A30922 A309 22
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving endothelial cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving endothelial cells). (HUVEC cells are human umbilical vein endothelial cells).	HUVEC	CD40 ICAM IL10 Rag1 Rag2 TNF	gb AJ300189 HS A30018 gb X06990 HSIC AM1 gb AF055467 AF 055467 gb M29474 HUM RAG1 gb AY011962 A Y011962 gb AJ270944 HS A27094
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The Jurkat cell line is a human T lymphocyte cell line available through the ATCC as cell line number TIB-152).	Jurkat	CD69 IL5 Rantes TNF	gb Z22576 HSCD 69GNA gb X12705 HSB CDFIA gb AF043341 AF 043341 gb AJ270944 HS A27094
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). (The Jurkat cell line is a human T lymphocyte cell line available through the ATCC as cell line number TIB-152).	Liver	CD25	gb X03137 HSIL 2RG7

202	HSDSB09	Immune	to, immune disorders involving cells of the hepatic system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the hepatic system). Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The Molt-4 cell line is a human T-cell line available through the ATCC as cell line number CRL-1582).	Molt4	CD28	gb AF222342 AF 222342
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the skin). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving the skin). (NHDF cells are normal human dermal fibroblasts).	NHDF	CD28 CD40 IL6	gb AF222342 AF 222342 gb AJ300189 HS A30018 gb X04403 HS26 KDAR
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the central nervous system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving the central nervous system). (The SK-N-MC neuroblastoma cell line is a cell line derived from human brain tissue and is available through the ATCC as cell line number HTB-10).	SK-N-MC neuroblastoma	c-maf CIS3 TNF	gb AF055377 AF 055377 gb AB006967 AB 006967 gb AJ270944 HS A27094

202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The SUPT cell line is a human T-cell line).	SUPT	TNF VCAM	gb AJ270944 HS A27094 gb A30922 A309 22
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The THP1 cell line is a human monocyte cell line available through the ATCC as cell line number TIB-202).	THP1	CCR3 CD40 GATA3 ICAM IL5 Rag2 VCAM	gb AB023887 AB 023887 gb AJ300189 HS A30018 gb X55037 HSG ATA3 gb X06990 HSIC AM1 gb X12705 HSB CDFIA gb AY011962 A Y011962 gb A30922 A309 22
202	HSDSB09	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The U937 cell line is a human monocyte cell line available through the ATCC as cell line number CRL-1593.2).	U937	IL1B	gb X02532 HSIL 1BR
247	HWHGZ51	Diabetes	A highly preferred indication is diabetes. Additional highly	Liver	GAPDH	

247	HWHGZ51	Immune	<p>preferred indications include complications associated with diabetes (e.g., diabetic retinopathy, diabetic nephropathy, kidney disease (e.g., renal failure, nephropathy and/or other diseases and disorders as described in the "Renal Disorders" section below), diabetic neuropathy, nerve disease and nerve damage (e.g., due to diabetic neuropathy), blood vessel blockage, heart disease, stroke, impotence (e.g., due to diabetic neuropathy or blood vessel blockage), seizures, mental confusion, drowsiness, nonketotic hyperglycemic-hyperosmolar coma, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section below), dyslipidemia, endocrine disorders (as described in the "Endocrine Disorders" section below), neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, and infection (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section below, especially of the urinary tract and skin). Highly preferred indications also include obesity, weight gain, and weight loss, as well as complications associated with obesity, weight gain, and weight loss. Preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating the above mentioned conditions, disorders, and diseases.</p> <p>Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving muscle tissues and the cardiovascular system (e.g. heart, lungs, circulatory system)). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving muscle tissue or the cardiovascular system). (AOSMC cells are human aortic smooth muscle cells).</p>	AOSMC	CD30 IL6	gb X04403 HS26 KDAR
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247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the cells of the gastrointestinal tract). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the gastrointestinal tract). (The Caco-2 cell line is a human colorectal adenocarcinoma cell line available through the ATCC as cell line number HTB-37).	Caco-2	Rag1	gb M29474 HUM RAG1
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the B-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving B-cells). (The Daudi cell line is a human B lymphoblast cell line available through the ATCC as cell line number CCL-213).	Daudi	CIS3 CXCR3 ICAM	gb AB006967 AB 006967 gb Z79783 HSCCK RL2 gb X06990 HSIC AM1
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The H9 cell line is a human T lymphocyte cell line available through the ATCC as cell line number HTB-176).	H9	IL5 VCAM VLA4	gb X12705 HSB CDFIA gb A30922 A309 22 gb X16983 HSIN TAL4
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the cells of the gastrointestinal tract). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving cells of the gastrointestinal tract). (The Caco-2 cell line is a human colorectal adenocarcinoma cell line available through the ATCC as cell line number HTB-37).	HEK293	Rag1 TNF	gb M29474 HUM RAG1 gb AJ270944 HS

				to, immune disorders involving epithelial cells or the renal system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving epithelial cells or the renal system). (The 293 cell line is a human embryonal kidney epithelial cell line available through the ATCC as cell line number CRL-1573).			A27094
247	HWHGZ51	Immune	HUVEC	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving endothelial cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving endothelial cells). (HUVEC cells are human umbilical vein endothelial cells).	CCR7 GATA3 TNF	gb X84702 HSD NABLR2 gb X55037 HSG ATA3 gb AJ270944 HS A27094	
247	HWHGZ51	Immune	Jurkat	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The Jurkat cell line is a human T lymphocyte cell line available through the ATCC as cell line number TIB-152).	Rag1 Rag2	gb M29474 HUM RAG1 gb AY011962 A Y011962	
247	HWHGZ51	Immune	Liver	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving cells of the hepatic system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not	CCR7 ICAM TNF VCAM	gb X84702 HSD NABLR2 gb X06990 HSIC AMI gb AJ270944 HS A27094 gb A30922 A309	

247	HWHGZ51	Immune	limited to, immune disorders involving cells of the hepatic system). Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The Molt-4 cell line is a human T-cell line available through the ATCC as cell line number CRL-1582).	Molt4	CD25 TNF VCAM	22 gb X03137 HSIL 2RG7 gb AJ270944 HS A27094 gb A30922 A309 22
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the skin). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving the skin). (NHDF cells are normal human dermal fibroblasts).	NHDF	CCR7 CD40 GATA3 HLA-c TNF	gb X84702 HSD NABLR2 gb AJ300189 HS A30018 gb X55037 HSG ATA3 gb AJ270944 HS A27094
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving the central nervous system). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving the central nervous system). (The SK-N-MC neuroblastoma cell line is a cell line derived from human brain tissue and is available through the ATCC as cell line number HTB-10).	SK-N-MC neuroblastoma	CIS3 LTBR Rag1	gb AB006967 AB 006967 gb AK027080 A K027080 gb M29474 HUM RAG1
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving T-cells). Highly preferred	SUPT	CCR4 Rag1 TNF	gb AB023888 AB 023888 gb M29474 HUM RAG1



247	HWHGZ51	Immune	embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving T-cells). (The SUPT cell line is a human T-cell line).			gb AJ270944 HS A27094
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The THP1 cell line is a human monocyte cell line available through the ATCC as cell line number TIB-202).	THP1	c-maf CCR7 CXCR3 IL5	gb AF055377 AF 055377 gb X84702 HSD NABLR2 gb Z79783 HSCK RL2 gb X12705 HSB CDFIA
247	HWHGZ51	Immune	Highly preferred indications include immunological disorders such as described herein under the heading "Immune Activity" and/or "Blood-Related Disorders" (particularly including, but not limited to, immune disorders involving monocytes). Highly preferred embodiments of the invention include methods of preventing, detecting, diagnosing, treating and/or ameliorating disorders of the immune system (particularly including, but not limited to, immune disorders involving monocytes). (The U937 cell line is a human monocyte cell line available through the ATCC as cell line number CRL-1593.2).	U937	CD69 ICAM TNF	gb Z22576 HSCD 69GNA gb X06990 HSIC AM1 gb AJ270944 HS A27094

Table 2 further characterizes certain encoded polypeptides of the invention, by providing the results of comparisons to protein and protein family databases. The first column provides a unique clone identifier, "Clone ID NO:", corresponding to a cDNA clone disclosed in Table 1A and/or Table 1B. The second column provides the unique contig identifier, "Contig ID:" which allows correlation with the information in Table 1B. The third column provides the sequence identifier, "SEQ ID NO:", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. The fifth column provides a description of the PFAM/NR hit identified by each analysis. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, score/percent identity, provides a quality score or the percent identity, of the hit disclosed in column five. Comparisons were made between polypeptides encoded by polynucleotides of the invention and a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM"), as described below.

The NR database, which comprises the NBRF PIR database, the NCBI GenPept database, and the SIB SwissProt and TrEMBL databases, was made non-redundant using the computer program nrdb2 (Warren Gish, Washington University in Saint Louis). Each of the polynucleotides shown in Table 1B, column 3 (e.g., SEQ ID NO:X or the 'Query' sequence) was used to search against the NR database. The computer program BLASTX was used to compare a 6-frame translation of the Query sequence to the NR database (for information about the BLASTX algorithm please see Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish and States, Nat. Genet. 3:266-272 (1993). A description of the sequence that is most similar to the Query sequence (the highest scoring 'Subject') is shown in column five of Table 2 and the database accession number for that sequence is provided in column six. The highest scoring 'Subject' is reported in Table 2 if (a) the estimated probability that the match occurred by chance alone is less than  $1.0e-07$ , and (b) the match was not to a known repetitive element. BLASTX returns alignments of short polypeptide segments of the Query and Subject sequences which share a high degree of similarity; these segments are known as High-Scoring Segment Pairs or HSPs. Table 2 reports the degree of similarity between the Query and the Subject for each HSP as a percent identity in Column 7. The percent identity is determined by dividing the number of exact matches between the two aligned sequences in the HSP, dividing by the number of Query amino acids in the HSP and multiplying by 100. The polynucleotides of SEQ ID NO:X which encode the polypeptide sequence that generates an HSP are delineated by columns 8 and 9 of Table 2.

The PFAM database, PFAM version 2.1, (Sonnhammer, Nucl. Acids Res., 26:320-322, 1998)) consists of a series of multiple sequence alignments; one alignment for each protein family. Each multiple sequence alignment is converted into a probability model called a Hidden

Markov Model, or HMM, that represents the position-specific variation among the sequences that make up the multiple sequence alignment (see, e.g., Durbin, et al., *Biological sequence analysis: probabilistic models of proteins and nucleic acids*, Cambridge University Press, 1998 for the theory of HMMs). The program HMMER version 1.8 (Sean Eddy, Washington University in Saint Louis) was used to compare the predicted protein sequence for each Query sequence (SEQ ID NO:Y in Table 1B) to each of the HMMs derived from PFAM version 2.1. A HMM derived from PFAM version 2.1 was said to be a significant match to a polypeptide of the invention if the score returned by HMMER 1.8 was greater than 0.8 times the HMMER 1.8 score obtained with the most distantly related known member of that protein family. The description of the PFAM family which shares a significant match with a polypeptide of the invention is listed in column 5 of Table 2, and the database accession number of the PFAM hit is provided in column 6. Column 7 provides the score returned by HMMER version 1.8 for the alignment. Columns 8 and 9 delineate the polynucleotides of SEQ ID NO:X which encode the polypeptide sequence which show a significant match to a PFAM protein family.

As mentioned, columns 8 and 9 in Table 2, "NT From" and "NT To", delineate the polynucleotides of "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth column. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the polynucleotides of SEQ ID NO:X delineated in columns 8 and 9 of Table 2. Also provided are polynucleotides encoding such proteins, and the complementary strand thereto.

The nucleotide sequence SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, the nucleotide sequences of SEQ ID NO:X are useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in ATCC Deposit No:Z. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to these polypeptides, or fragments thereof, and/or to the polypeptides encoded by the cDNA clones identified in, for example, Table 1A and/or 1B.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the

generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and a predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing cDNA ATCC Deposit No:Z (e.g., as set forth in columns 2 and 3 of Table 1A and/or as set forth, for example, in Table 1B, 6, and 7). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

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Table 2

cDNA Clone ID	Contig ID:	SEQ ID NO:X	Analysis Method	PFam/NR Description	PFam/NR Accession Number	Score/Percent Identity	NT From	NT To
H2CBU83	884134	11	WUblastx .64	(Q9NYD1) G-PROTEIN-COUPLED RECEPTOR 48.	Q9NYD1	100%	10	777
H2CBU83	745366	262	WUblastx .64	(Q9NYD1) G-PROTEIN-COUPLED RECEPTOR 48.	Q9NYD1	98% 44% 100%	291 151 10	776 204 297
HACBD91	637482	13	WUblastx .64	NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) chain NDUFB4 - human	pir JE0383 JE0383	100% 95%	211 1306	357 1368
HACCI17	891114	14	HMMER 2.1.1	PFAM: PMP-22/EMP/MP20/Claudin family	PF00822	142.7	470	1003
			WUblastx .64	(Q8WUW3) Hypothetical 27.7 kDa protein (Fragment).	Q8WUW3	100%	317	1114
HACCI17	731877	263	HMMER 2.1.1	PFAM: PMP-22/EMP/MP20/Claudin family	PF00822	35.6	144	329
			WUblastx .64	(Q8WUW3) Hypothetical 27.7 kDa protein (Fragment).	Q8WUW3	80% 57% 90% 30% 75% 100%	24 454 1 66 535 311	329 495 96 296 786 619

HAGA26	561996	15	WUblastx .64	(Q9UKG4) NA+/SULFATE COTRANSPORTER SUT-1.	Q9UKG4	99% 93%	414 2	1001 433
HAHDB16	635412	18	WUblastx .64	(Q9GMK2) HYPOTHETICAL 10.0 KDA PROTEIN.	Q9GMK2	75% 69%	641 762	522 634
HAICP19	422672	19	WUblastx .64	(Q9H173) SIL1 PROTEIN PRECURSOR.	Q9H173	100%	83	1465
HAJAN23	1352364	21	WUblastx .64	(Q9HCC0) NON-BIOTIN CONTAINING SUBUNIT OF 3- METHYLCROTONYL- COA CARBOX	Q9HCC0	100%	109	1797
HAJAN23	872551	265	HMMER 2.1.1	PFAM: Carboxyl transferase domain	PF01039	126.6	294	617
			WUblastx .64	(Q9HCC0) NON-BIOTIN CONTAINING SUBUNIT OF 3- METHYLCROTONYL- COA CARBOX	Q9HCC0	91% 96%	120 557	665 1807
HAJBR69	638516	22	WUblastx .64	(Q9JIG5) UBIQUITIN SPECIFIC PROTEASE (FRAGMENT).	Q9JIG5	69%	677	48
HAMFE15	905695	23	HMMER 2.1.1	PFAM: Diacylglycerol kinase catalytic domain (presumed)	PF00781	22.9	1807	1956
			WUblastx .64	(Q9NP48) PUTATIVE LIPID KINASE (CDNA FLJ10842 FIS, CLONE	Q9NP48	93%	1495	2757

HAMFE15	823350	266	WUblastx .64	NT2RP4001343 (Q9NP48) PUTATIVE LIPID KINASE (CDNA FLJ10842 FIS, CLONE NT2RP4001343	Q9NP48	93%	1503	2756
HAMGR28	892971	24	WUblastx .64	(AAH07438) Similar to RIKEN cDNA 2610511E22 gene.	AAH07438	100%	59	823
HAMGR28	748223	267	WUblastx .64	(AAH07438) Similar to RIKEN cDNA 2610511E22 gene.	AAH07438	100% 100%	569 1	766 567
HAPBS03	656755	25	WUblastx .64	(Q99KG1) SIMILAR TO HETEROGENEOUS NUCLEAR RIBONUCLEOPROTEIN R (FRAGME	Q99KG1	51% 85% 62%	59 593 643	175 655 777
HAPOM49	769555	27	WUblastx .64	(Q9BZM1) GROUP XII SECRETED PHOSPHOLIPASE A2.	Q9BZM1	99%	251	817
HAPOM49	722386	268	WUblastx .64	(Q9BZM1) GROUP XII SECRETED PHOSPHOLIPASE A2.	Q9BZM1	100% 100%	251 454	451 816
HAPUC89	834358	28	WUblastx .64	(Q9BUM1) UNKNOWN (PROTEIN FOR IMAGE:3050476) (FRAGMENT).	Q9BUM1	99%	109	804
HATBR65	635514	29	WUblastx .64	(Q96NR6) CDNA FLJ30278 fis, clone BRACE2002755.	Q96NR6	42% 64%	750 617	806 751
HAUAI83	639009	30	WUblastx	(BAB27250) 13 days	BAB27250	88%	160	399

				.64	embryo liver cDNA, RIKEN full-le			90%	25	84
HAUIA183	383592	269	WUblastx .64	(BAB27250) 13 days embryo liver cDNA, RIKEN full-le	BAB27250			100%	489	557
HBGBA69	1352289	32	WUblastx .64	(Q8WVV8) Hypothetical 22.4 kDa protein (Fragment).	Q8WVV8			100%	406	723
HBGBA69	709658	270	WUblastx .64	(Q8WVV8) Hypothetical 22.4 kDa protein (Fragment).	Q8WVV8			100%	220	843
HBGNU56	1352412	33	WUblastx .64	(Q96DB9) FXYD domain-containing ion transport regulator 5 p	FXYS_HUMAN			78% 100%	158 211	226 780
HBGNU56	1094642	271	HMMER 2.1.1	PFAM: ATP1G1/PLM/MAT8 family	PF02038			70.5	475	609
			WUblastx .64	(Q96DB9) FXYD domain-containing ion transport regulator 5 p	FXYS_HUMAN			100%	79	612
HBGNU56	1050255	272	HMMER 2.1.1	PFAM: ATP1G1/PLM/MAT8 family	PF02038			70.5	521	655
			WUblastx .64	(Q96DB9) FXYD domain-containing ion transport regulator 5 p	FXYS_HUMAN			100%	125	658
HBIAE26	514418	34	WUblastx .64	(AAK55521) PRO0764.	AAK55521			83% 65%	1009 983	974 744
HBINS58	1352386	35	WUblastx .64	(Q9D6W7) 2310047N01RIK	Q9D6W7			81%	57	578



HBINS58	961712	273	WUblastx .64	PROTEIN. (Q9D6W7) 2310047N01RIK PROTEIN.	Q9D6W7	80%	71	589
HBINS58	892924	274	WUblastx .64	(Q9D6W7) 2310047N01RIK PROTEIN.	Q9D6W7	79%	100	579
HBJFU48	460392	36	WUblastx .64	(Q9P195) PRO1722.	Q9P195	63% 73% 64%	716 819 667	660 718 533
HCE2F54	634016	39	HMMER 2.1.1	PFAM: Histone-like transcription factor (CBF/NF-Y) and archaeal histone	PF00808	19	868	1005
			WUblastx .64	(AAH07642) Unknown (protein for IMAGE:3534358) (Fra	AAH07642	82%	298	1122
HCE3G69	728432	40	WUblastx .64	(Q9H0K7) HYPOTHETICAL 12.4 KDA PROTEIN (UNKNOWN) (PROTEIN FOR MGC:303	Q9H0K7	100%	1294	1647
HCE3G69	494346	275	WUblastx .64	(Q9H0K7) HYPOTHETICAL 12.4 KDA PROTEIN (UNKNOWN) (PROTEIN FOR MGC:303	Q9H0K7	100%	1295	1648
HCE5F43	612796	41	WUblastx	(Q9H8M7) CDNA	Q9H8M7	100%	9	53

				.64	FLJ13397 FIS, CLONE PLACE1001351.		100%	56	928
HCEFB80	1143407	42	WUblastx .64	(Q96FR3) Unknown (protein for MGC:18083).	Q96FR3	100%	1785	1979	
HCEFB80	1046853	276	WUblastx .64	(Q96FR3) Unknown (protein for MGC:18083).	Q96FR3	100%	1777	1971	
HCEWE20	543370	44	WUblastx .64	(Q9P1J1) PRO1546.	Q9P1J1	76% 79%	501 601	551 717	
HCFOM18	553582	45	WUblastx .64	(Q9H728) CDNA: FLJ21463 FIS, CLONE COL04765.	Q9H728	60%	621	490	
HCGMD59	636078	46	WUblastx .64	catalase (EC 1.11.1.6) - Campylobacter jejuni	pir 40767 40767	97%	296	186	
HCNDR47	1016919	47	WUblastx .64	(BAB84904) FLJ00149 protein (Fragment).	BAB84904	93% 42%	969 180	1154 263	
HCNDR47	863677	277	WUblastx .64	(Q24333) ELASTIN LIKE PROTEIN (FRAGMENT).	Q24333	57%	42	197	
HCNDR47	874128	278	WUblastx .64	(BAB84904) FLJ00149 protein (Fragment).	BAB84904	93%	148	333	
HCWDS72	707833	52	WUblastx .64	conserved hypothetical protein PA1527 [imported] - Pseudomonas aeruginosa (strain PAO1)	pir D83454 D83454	77%	318	4	
HCWKCI5	553621	53	WUblastx .64	(Q9NX85) CDNA FLJ20378 FIS, CLONE KAIA0536.	Q9NX85	77% 56% 63%	538 710 708	419 663 532	
HCWUM50	639037	54	WUblastx .64	(Q9NWD1) HYPOTHETICAL 61.6 KDA PROTEIN.	Q9NWD1	94% 73%	2 1103	175 1303	

HDABR72	1301517	55	WUblastx .64	(Q9BTK4) UNKNOWN (PROTEIN FOR MGC:4663).	Q9BTK4	100%	695	886
HDABR72	748225	280	HMMER 2.1.1	PFAM: Cytochrome P450	PF00067	21.7	145	282
			WUblastx .64	(Q9BTK4) UNKNOWN (PROTEIN FOR MGC:4663).	Q9BTK4	100%	690	881
HDPBA28	1062783	56	WUblastx .64	(Q9UKY2) ADIPOCYTE-DERIVED LEUCINE AMINOPEPTIDASE.	Q9UKY2	99%	259	3081
HDPBA28	866429	281	HMMER 2.1.1	PFAM: Peptidase family M1	PF01433	613.6	228	1391
			WUblastx .64	(Q9UKY2) ADIPOCYTE-DERIVED LEUCINE AMINOPEPTIDASE.	Q9UKY2	99%	69	2891
HDPBI32	1352360	57	WUblastx .64	(O88407) NEURAL MEMBRANE PROTEIN 35.	O88407	92%	37	984
HDPBI32	862851	282	WUblastx .64	(O88407) NEURAL MEMBRANE PROTEIN 35.	O88407	95% 89%	599 103	1051 603
HDPBI32	590733	283	HMMER 2.1.1	PFAM: Uncharacterized protein family	PF01027	126.8	51	461
HDPCJ91	740748	58	WUblastx .64	(Q9H387) PRO2550.	Q9H387	53% 56%	2369 2377	2407 2676
HDPCL63	1019008	59	WUblastx .64	(Q9Y519) HYPOTHETICAL 42.3	Q9Y519	99%	14	835

HDPCL63	847045	284	WUblastx .64	KDA PROTEIN. (Q9Y519) HYPOTHETICAL 42.3 KDA PROTEIN.	Q9Y519	97%	2	730
HDPGT01	771583	61	WUblastx .64	(Q9Y2B3) LCAT-LIKE PROTEIN (LLPL).	Q9Y2B3	100% 100%	8 264	262 1244
HDPJM30	879325	63	WUblastx .64	(O94759) LONG TRANSIENT RECEPTOR POTENTIAL CHANNEL 2 (LTPC	TRL2_HUMAN	99%	17	1633
HDPJM30	603517	286	WUblastx .64	(O94759) LONG TRANSIENT RECEPTOR POTENTIAL CHANNEL 2 (LTPC	TRL2_HUMAN	89% 96% 98%	416 378 1	1312 530 378
HDPND46	637586	64	WUblastx .64	(Q9BR26) DJ257E24.3 (NOVEL PROTEIN) (FRAGMENT).	Q9BR26	81%	12	1466
HDPOJ08	731863	65	WUblastx .64	(Q9H7X1) CDNA FLJ14153 FIS, CLONE NT2RM1000092, WEAKLY SIMILAR TO MUL	Q9H7X1	84% 30% 99%	524 315 12	904 479 524
HDPPN86	1037893	66	WUblastx .64	(Q9BVN4) HYPOTHETICAL 59.4 KDA PROTEIN.	Q9BVN4	77% 100% 97% 42% 47% 98%	5063 919 1942 4835 4983 4611	5194 1308 2175 4891 5045 4799

HDPPN86	895711	287	WUblastx .64	(Q9BVN4) HYPOTHETICAL 59.4 KDA PROTEIN.	Q9BVN4	98%	909	1817
HDPSB18	1043263	67	WUblastx .64	(Q9NX17) CDNA FLJ20489 FIS, CLONE KAT08285.	Q9NX17	66% 46%	3407 2573	3150 2478
HDPSB18	732097	290	WUblastx .64	(Q9NX17) CDNA FLJ20489 FIS, CLONE KAT08285.	Q9NX17	41% 66%	863 813	789 556
HDPSH53	1309174	68	WUblastx .64	(Q9EPY0) CASPASE RECRUITMENT DOMAIN PROTEIN 9.	Q9EPY0	59% 88%	262 1023	456 1184
HDPSH53	1040056	291	WUblastx .64	(Q9H257) CASPASE RECRUITMENT DOMAIN PROTEIN 9.	Q9H257	100% 92% 25% 100%	1131 301 1518 1010	1184 423 1610 1129
HDPSH53	882768	292	WUblastx .64	(AAH08877) Caspase recruitment domain protein 9.	AAH08877	98%	316	480
HDPSP01	1352280	69	WUblastx .64	(Q9BR97) UNKNOWN (PROTEIN FOR MGC:10763).	Q9BR97	93% 94% 41%	1671 184 2196	1718 1674 2276
HDPSP01	689129	293	WUblastx .64	(Q9BR97) UNKNOWN (PROTEIN FOR MGC:10763).	Q9BR97	90% 98% 100%	227 1078 1664	1114 1668 1744
HDPSP54	744440	70	WUblastx .64	(BAB85063) CDNA FLJ23790 fis, clone HEP21466.	BAB85063	99%	2	307
HDPUH26	866433	71	WUblastx .64	(Q8VHE7) Hypothetical 67.5 kDa protein.	Q8VHE7	80% 69%	261 162	1733 290

HDPWU68	812737	72	HMMER 2.1.1	PFAM: Immunoglobulin domain	PF00047	38.9	844	1005
			WUblastx .64	(Q9Y286) QA79 MEMBRANE PROTEIN, ALLELIC VARIANT AIRM-1B PRECURSOR.	Q9Y286	100%	40	1440
HDPWU34	630354	73	HMMER 2.1.1	PFAM: POT family	PF00854	77.2	432	857
			WUblastx .64	(Q9P2X9) PEPTIDE TRANSPORTER 3.	Q9P2X9	100%	3	1091
HDPXY01	879048	74	WUblastx .64	hypothetical protein DKFZp434A139.1 - human (fragments)	pir T43490 T43490	93%	3	743
HDPXY01	904768	296	WUblastx .64	hypothetical protein DKFZp434A139.1 - human (fragments)	pir T43490 T43490	97%	10	921
HDPXY01	895715	298	WUblastx .64	(O93251) ALPHA 1 TYPE I COLLAGEN.	O93251	29% 35%	643 268	1419 447
HDTBV77	785879	75	WUblastx .64	(Q9BT94) UNKNOWN (PROTEIN FOR MGC:10848).	Q9BT94	99% 69%	65 2131	2137 2169
HDTDQ23	1306984	76	WUblastx .64	calcium-binding protein (clone pMP41) - mouse (fragment)	pir S04970 S04970	100%	1611	1709
HDTDQ23	879009	299	WUblastx .64	calcium-binding protein (clone pMP41) - mouse (fragment)	pir S04970 S04970	100%	1623	1721
HDTDQ23	751707	300	WUblastx .64	calcium-binding protein (clone pMP41) - mouse (fragment)	pir S04970 S04970	100%	1623	1721

HE2DE47	619852	77	WUblastx .64	(Q9NZN8) NOT2P (CCR4-NOT TRANSCRIPTION COMPLEX, SUBUNIT 2).	Q9NZN8	99%	808	2427
HE2NV57	740750	78	WUblastx .64	(Q9UGV6) BK445C9.3 (HIGH-MOBILITY GROUP (NONHISTONE CHROMOSOMAL) PROT	Q9UGV6	31% 66%	321 71	866 106
HE2PH36	570903	79	WUblastx .64	(AAH07609) Similar to hypothetical protein PRO1722.	AAH07609	56% 90% 68%	1359 1524 1484	1285 1492 1353
HE8DS15	847060	80	WUblastx .64	(Q9WVT0) SEVEN TRANSMEMBRANE RECEPTOR.	Q9WVT0	80% 24% 87%	1 48 269	270 146 985
HE9CO69	596829	81	WUblastx .64	(O95772) H_NH1021A08.1 PROTEIN (UNKNOWN) (PROTEIN FOR MGC:14607) (SIM	O95772	82%	25	270
HE9OW20	1352337	83	WUblastx .64	(CAC41349) Alpha2- glucosyltransferase.	CAC41349	95%	129	1151
HE9OW20	838598	302	WUblastx .64	(CAC41349) Alpha2- glucosyltransferase.	CAC41349	99%	142	996
HE9OW20	834400	303	WUblastx .64	(CAC41349) Alpha2- glucosyltransferase.	CAC41349	93% 95%	129 449	497 1051
HEEAG23	684254	84	HMMER 2.1.1	PFAM: emp24/gp25L/p24 family	PF01105	36.2	63	185
			WUblastx	(AAH23041) Similar to	AAH23041	100%	114	185

				.64	RIKEN cDNA 2400003B06 gene.		99%	406	780
HEOMQ63	603533	85		WUblastx .64	(Q9BQM3) DJ842G6.1.1 (NOVEL PROTEIN) (FRAGMENT).	Q9BQM3	100% 100% 99%	1036 592 635	1293 639 937
HFABG18	847073	87		WUblastx .64	(Q9QZE9) TM6P1.	Q9QZE9	95% 88%	53 237	253 797
HFABH95	566712	88		WUblastx .64	(Q9QZH5) PUTATIVE PHOSPHATE/PHOSPHO ENOLPYRUVATE TRANSLOCATOR.	Q9QZH5	88% 65%	513 9	944 77
HFAEF57	534142	89		WUblastx .64	(Q9HBN2) HYPOTHETICAL 15.8 KDA PROTEIN.	Q9HBN2	47%	601	425
HFCEB37	411345	90		WUblastx .64	(Q9NYC6) NEURONAL SPECIFIC TRANSCRIPTION FACTOR DAT1.	Q9NYC6	94%	4	204
HFGAD82	513669	92		WUblastx .64	membrane glycoprotein M6 - mouse	pir I78556 I78556	92%	249	410
HFIIIN69	1011487	93		WUblastx .64	(Q9UI86) PRO0113.	Q9UI86	55%	1448	1281
HFIIIN69	874248	306		WUblastx .64	(Q9UI86) PRO0113.	Q9UI86	54%	671	501
HFIIUR10	532060	94		WUblastx .64	(AAK55521) PRO0764.	AAK55521	47% 75%	369 497	307 411
HFKFG02	634743	95		WUblastx .64	ISOFORM OAT1.2 OF O95742	tr_vs O95742- 01 O95742	89% 100%	11 253	265 564
HFTBM50	545012	96		WUblastx .64	(Q9H8P0) CDNA FLJ13352 FIS, CLONE	Q9H8P0	100% 91%	23 198	229 524



					OVARC1002165, WEAKLY SIMILAR TO 3-O							
HFXHK73	609826	99	WUblastx .64		(Q9H960) CDNA FLJ12988 FIS, CLONE NT2RP3000080.	Q9H960	58% 50%	1164 1749	1042 1714			
HFXJX44	701988	100	WUblastx .64		(Q9N083) UNNAMED PORTEIN PRODUCT.	Q9N083	57%	1378	1082			
HFXKY27	634161	101	WUblastx .64		(Q9P147) PRO2822.	Q9P147	86% 70%	812 928	768 815			
HGBHI35	570262	102	HMMER 2.1.1		PFAM: Enoyl-CoA hydratase/isomerase family	PF00378	184.6	213	722			
			WUblastx .64		(AAH25104) Similar to RIKEN cDNA 1300017C12 gene.	AAH25104	91%	225	962			
HHBCS39	1003028	104	WUblastx .64		(Q9H763) CDNA: FLJ21269 FIS, CLONE COL01745.	Q9H763	98%	17	601			
HHBCS39	883427	307	WUblastx .64		(Q9H763) CDNA: FLJ21269 FIS, CLONE COL01745.	Q9H763	98%	63	647			
HHEAA08	638231	105	WUblastx .64		(Q9BVD9) UNKNOWN (PROTEIN FOR MGC:5149).	Q9BVD9	61% 74%	1923 2147	1870 1923			
HHFFJ48	634521	107	WUblastx .64		(Q9CWA7) 0610010F05RIK PROTEIN (FRAGMENT).	Q9CWA7	49%	1362	1598			
HHGBO91	520198	109	WUblastx		(Q96NR6) CDNA	Q96NR6	86%	622	687			

				.64	FLJ30278 fis, clone BRACE2002755.			66%	531	620
HHGCM76	662329	111	WUblastx .64	(Q96FV2) Unknown (protein for IMAGE:3945715) (Fragment).	Q96FV2		94%	7	114	353
HHGCM76	383547	310	WUblastx .64	(Q96FV2) Unknown (protein for IMAGE:3945715) (Fragment).	Q96FV2		98%	378	536	496
HHPEN62	695134	113	HMMER 2.1.1	PFAM: Peptidase family M20/M25/M40	PF01546		148.9	510	1535	
			WUblastx .64	(Q96KN2) Glutamate carboxypeptidase-like protein 2.	Q96KN2		99%	183	1706	
HJABB94	456466	114	WUblastx .64	(Q9BWW3) PROTEIN KINASE NYD-SP15.	Q9BWW3		100%	8	250	
							38%	1127	1192	
HJACG02	1307789	115	WUblastx .64	(Q9HD89) CYSTEINE- RICH SECRETED PROTEIN (C/EBP- EPSILON REGULATED MYEL	Q9HD89		94%	1227	1523	
							100%	66	389	
HJACG02	509948	311	WUblastx .64	(Q9HD89) CYSTEINE- RICH SECRETED PROTEIN (C/EBP- EPSILON REGULATED MYEL	Q9HD89		100%	47	370	
HJACG30	895505	116	WUblastx	(Q9UM21) UDP-	Q9UM21		96%	291	389	





				.64	F16H11.1 - Caenorhabditis elegans			32%	135	713
HKGDL36	877489	125	WUblastx .64	(Q9UHG2) PROSAAS PRECURSOR (GRANIN- LIKE NEUROENDOCRINE PEPTIDE PRECUR	Q9UHG2	99%	53	832		
HKGDL36	704088	323	WUblastx .64	(Q9UHG2) PROSAAS PRECURSOR (GRANIN- LIKE NEUROENDOCRINE PEPTIDE PRECUR	Q9UHG2	82% 49%	99 55	830 555		
HKISB57	625956	126	WUblastx .64	(Q8WWW1) Smoothelin- B3.	Q8WWW1	28% 100% 98% 27% 26% 44%	262 201 1107 271 532 954	582 1013 1256 480 966 1052		
HKMMW74	581399	127	WUblastx .64	(Q8WY51) HC6.	Q8WY51	73%	1784	1662		
HLDNA86	1352197	128	WUblastx .64	(Q9BQB6) UNKNOWN (PROTEIN FOR MGC:11276) (PROTEIN FOR IMAGE:3455200).	Q9BQB6	100%	238	726		
HLDNA86	535730	324	WUblastx .64	(Q9BQB6) UNKNOWN (PROTEIN FOR MGC:11276) (PROTEIN FOR IMAGE:3455200).	Q9BQB6	72% 83% 100%	326 217 45	424 339 218		
HLDQR62	753742	130	WUblastx .64	(Q9NQW2) PROGRESSIVE	Q9NQW2	100% 99%	41 376	382 1002		

HLDR48	740755	131	WUblastx .64	ANKYLOSIS-LIKE PROTEIN. (O75477) KE04P.	O75477	100%	105	1142
HLICQ90	791828	134	WUblastx .64	(Q96N65) CDNA FLJ13149 fis, clone MESAN2000092, moderately similar to	Q96N65	95% 93%	571 59	636 616
HLQDR48	1307726	135	WUblastx .64	(Q9NQZ1) HEPATOCELLULAR CARCINOMA ASSOCIATED PROTEIN TD26.	Q9NQZ1	86%	296	406
HLQDR48	619979	325	WUblastx .64	(AAH24408) Hypothetical 20.3 kDa protein (Fragment)	AAH24408	65% 100%	54 675	572 701
HLTHR66	699812	136	HMMER 2.1.1	PFAM: PAP2 superfamily	PF01569	22.3	35	151
			WUblastx .64	(Q9D4F2) 4932443D16RIK PROTEIN.	Q9D4F2	93%	2	229
HLTIP94	1087335	137	WUblastx .64	(Q96DH6) Hypothetical 35.2 kDa protein.	Q96DH6	80%	579	740
HLTIP94	1047690	327	HMMER 2.1.1	PFAM: RNA recognition motif. (a.k.a. RRM, RBD, or RNP domain)	PF00076	143.1	40	-172
			WUblastx .64	(Q96DH6) Hypothetical 35.2 kDa protein.	Q96DH6	99%	123	776
HLWAA17	629552	138	WUblastx .64	(Q9NY26) IRT1 PROTEIN (SIMILAR TO	Q9NY26	94% 100%	226 85	960 123

					ZINC/IRON REGULATED TRANSPORTER-LIK							
HLWBK05	765310	139	WUblastx .64	(Q9CUS9) 4833416I09RIK PROTEIN (FRAGMENT).	Q9CUS9	84%	10	1173				
HLWBY76	797609	140	WUblastx .64	(AAH06651) Similar to hypothetical protein FLJ23153	AAH06651	76%	6	1127				
HLYAN59	553507	328	WUblastx .64	(AAL79706) Hypothetical 9.4 kDa protein.	AAL79706	85% 93% 82%	624 639 617	719 728 721				
HLYES38	638042	145	WUblastx .64	(O95662) POT. ORF VI (FRAGMENT).	O95662	81% 72% 72% 75% 33%	743 281 306 466 145	856 313 524 735 243				
HMADK33	561941	146	WUblastx .64	hypothetical protein DKFZp761P2414.1 - human	pir T47139 T47139	87% 100% 94%	394 152 228	417 232 395				
HMADS41	596831	147	WUblastx .64	(AAH07725) Ceroid- lipofuscinosis, neuronal 8 (epile	AAH07725	92% 100%	186 427	449 1041				
HMAMI15	1352406	148	WUblastx .64	(AAL84703) Citrate lyase beta subunit.	AAL84703	99%	4	1023				
HMAMI15	1049263	329	WUblastx .64	(AAL84703) Citrate lyase beta subunit.	AAL84703	100% 79%	3 372	440 920				
HMCIFY13	635301	149	WUblastx .64	(Q8WZ81) Chromosome 17 open reading frame 26.	Q8WZ81	95%	36	737				

HMEED18	560775	151	WUblastx .64	(Q9H651) CDNA: FLJ22604 FIS, CLONE HSI04630 (BBP-LIKE PROTEIN 2).	Q9H651	99%	34	696
HMSDL37	973996	154	WUblastx .64	(Q9H743) CDNA: FLJ21394 FIS, CLONE COL03536.	Q9H743	66% 56%	1189 931	1497 1110
HMSDL37	895429	330	WUblastx .64	(Q9H743) CDNA: FLJ21394 FIS, CLONE COL03536.	Q9H743	64% 56%	1186 928	1494 1107
HMSDL37	904241	331	WUblastx .64	hypothetical protein 3 - human	pir E41925 E41925	50% 47%	421 161	350 39
HMSFI26	560229	155	WUblastx .64	(Q14713) POT. ORF V.	Q14713	57% 39%	1075 1041	1019 805
HMTBI36	1301451	157	WUblastx .64	(Q9VZF8) CG1332 PROTEIN.	Q9VZF8	56% 36% 40% 35% 27% 40%	958 2488 376 2341 2494 712	2556 3024 879 2550 2622 834
HMTBI36	866466	333	HMMER 2.1.1	PFAM: WD domain, G- beta repeat	PF00400	45.8	2490	2600
			WUblastx .64	(Q9VZF8) CG1332 PROTEIN.	Q9VZF8	56% 36% 40% 35% 27% 40%	957 2487 375 2340 2493 711	2555 3023 878 2549 2621 833
HMVBS81	639203	158	WUblastx .64	(O95070) 54TMP.	O95070	100%	10	450



HMWFT65	562063	160	WUblastx .64	(Q96AZ2) Similar to hypothetical protein FLJ21463.	Q96AZ2	67%	1342	1205
HNFFC43	753337	162	WUblastx .64	(Q969J4) Lipocalin-1 interacting membrane receptor (Lipocalin- interac	Q969J4	97% 66% 87% 99%	319 428 651 903	453 769 839 1517
HNFIY77	634551	164	WUblastx .64	(Q8WXE6) KCCR13L.	Q8WXE6	96% 99%	866 105	1030 866
HNFJF07	577013	165	WUblastx .64	(Q8WYX2) Hypothetical 14.1 kDa protein.	Q8WYX2	65%	585	457
HNGEP09	499076	167	WUblastx .64	(AAK55521) PRO0764.	AAK55521	57% 53% 50%	965 1021 867	861 977 715
HNGIJ31	519120	169	WUblastx .64	(Q9N083) UNNAMED PORTEIN PRODUCT.	Q9N083	73% 54% 66%	566 615 454	610 725 561
HNGJE50	561568	170	WUblastx .64	(Q9HBS7) HYPOTHETICAL 14.2 KDA PROTEIN.	Q9HBS7	64% 62%	1028 919	945 734
HNGOI12	1041375	172	WUblastx .64	collagen alpha 1(VIII) chain precursor - rabbit	pir A34246 A34246	31%	1067	2092
HNHEU93	634851	173	WUblastx .64	(Q9H387) PRO2550.	Q9H387	67%	741	418
HNHFM14	664507	174	WUblastx .64	(Q9N8S9) POSSIBLE (HHV-6) U1102, VARIANT A DNA, COMPLETE VIRION GENOM	Q9N8S9	74% 45% 63% 79% 76%	6 17 11 9 9	122 223 124 110 122
HNHNB29	895462	176	WUblastx	(Q9P195) PRO1722.	Q9P195	79%	1543	1674

HNHOD46	843488	177	.64 WUblastx .64	(O60448) NEURONAL THREAD PROTEIN AD7C-NTP.	O60448		75%	1398	1553
								334	552
								646	921
								645	713
								844	894
								331	498
								353	625
								828	917
								721	792
								781	915
								558	791
								401	595
								283	552
								379	462
								486	839
HNTBI26	1310821	178	WUblastx .64	(Q96F65) Similar to RIKEN cDNA 0610031J06 gene (Fragment).	Q96F65		99%	145	987
								1091	1201
								7	150
HNTBI26	796807	336	WUblastx .64	(Q96F65) Similar to RIKEN cDNA 0610031J06 gene (Fragment).	Q96F65		94%	516	992
								149	544
								1096	1206
								11	154
HNTBI26	590738	337	WUblastx .64	(Q96F65) Similar to RIKEN cDNA 0610031J06 gene (Fragment).	Q96F65		70%	824	973
								285	887
								133	378
								1077	1187
								1	138
HNTBL27	545534	179	WUblastx .64	(Q96AA3) Putative endoplasmic reticulum multispan transmembrane	Q96AA3		98%	243	500
								13	168
								646	711

HNTCE26	1160395	180	HMMER 2.1.1	prote PFAM: 7 transmembrane receptor (rhodopsin family)	PF00001	96%	13	261
						137.5	282	1037
			WUblastx .64	(Q9H1Y3) DJ317G22.2 (ENCEPHALOPSIN) (PANOPSIN).	Q9H1Y3	100%	111	1316
HNTCE26	853373	338	HMMER 2.1.1	PFAM: 7 transmembrane receptor (rhodopsin family)	PF00001	23.2	63	218
			WUblastx .64	(Q9H1Y3) DJ317G22.2 (ENCEPHALOPSIN) (PANOPSIN).	Q9H1Y3	95% 100%	370 12	495 377
HNTNC20	700627	181	WUblastx .64	(AAH24118) Similar to Unknown (protein for IMAGE:44	AAH24118	57%	252	776
HNTSY18	1041383	183	WUblastx .64	(Q9XSV8) SCO- SPONDIN (FRAGMENT).	Q9XSV8	70% 63% 37% 31% 29% 28% 30% 36% 30% 29% 29% 41% 50% 78% 26%	51 1204 54 66 824 42 66 48 416 635 1078 1482 1101 539 530	644 1236 596 803 931 596 863 662 922 1276 1356 1517 1157 1201 892

HNTSY18	897950	340	WUblastx .64	(Q9GMX5) HYPOTHETICAL 12.9 KDA PROTEIN.	Q9GMX5	36%	228	584 1198 551 537 329 389 329 581 1523 1076
HODDN92	422913	186	WUblastx .64	(Q9H1S5) BA110H4.2 (SIMILAR TO MEMBRANE PROTEIN).	Q9H1S5	100%	1119	201
HOFMQ33	1184465	188	WUblastx .64	(O15232) MATRILIN-3 PRECURSOR.	MTN3_HUMAN	85%	43	1500
HOFMQ33	919896	341	HMMER 2.1.1	PFAM: von Willebrand factor type A domain	PF00092	189.8	288	815
HOFMQ33	906694	342	HMMER 2.1.1	PFAM: von Willebrand factor type A domain	PF00092	162.2	318	737
HOFMQ33	902639	343	WUblastx .64	(O15232) MATRILIN-3 PRECURSOR.	MTN3_HUMAN	81%	72	857
HOFMQ33	702186	344	WUblastx	(O15232) MATRILIN-3 PRECURSOR.	MTN3_HUMAN	81%	1584	877
HOFMQ33	702186	344	WUblastx	(Q8WUF2) Hypothetical	Q8WUF2	88%	937	911

HOHBY44	873264	189	.64	23.7 kDa protein. (O60565) GREMLIN (DRM).	O60565	99%	914	327
HOQBJ82	1352356	190	WUblastx .64	(CAC37794) H-(3)mbt- like protein.	CAC37794	100%	170	721
HOQBJ82	858338	347	WUblastx .64	(Q9BQI2) HYPOTHETICAL 69.3 KDA PROTEIN.	Q9BQI2	100%	324	2414
HOQBJ82	857453	348	HMMER 2.1.1	PFAM: SET domain	PF00856	211.5	100	489
			WUblastx .64	(O96028) WHSC1 PROTEIN.	O96028	98%	61	1029
HOSDJ25	854234	192	WUblastx .64	(Q9D8Y9) 1810018L05RIK PROTEIN.	Q9D8Y9	49%	2	166
HOUQC17	429229	193	HMMER 2.1.1	PFAM: Reprolysin family propeptide	PF01562	85%	468	593
			WUblastx .64	(P97857) ADAM-TS 1 PRECURSOR (EC 3.4.24.-) (A DISINTEGRIN A	ATSI_MOUSE	86%	143	544
HPEAD79	520202	194	WUblastx .64	(Q96NR6) CDNA FLJ30278 fis, clone BRACE2002755.	Q96NR6	76.2	-115	-351
HPIBO15	1310868	195	WUblastx .64	(Q9CQS3) 1110018M03RIK PROTEIN.	Q9CQS3	81%	508	3408
HPIBO15	590741	350	WUblastx .64	(Q9CQS3) 1110018M03RIK PROTEIN.	Q9CQS3	48%	498	806
						93%	128	757
						88%	127	402
						95%	507	722
						97%	401	508

HPJBI33	685699	196	WUblastx .64	(O60448) NEURONAL THREAD PROTEIN AD7C-NTP.	O60448	49% 33% 51% 35% 33% 51% 59% 52% 34% 50% 47%	617 633 24 570 1317 155 154 137 41 3 886	934 890 122 872 1415 256 234 256 256 146 942
HPJCL22	1146674	198	WUblastx .64	(Q9GKV3) HYPOTHETICAL 41.8 KDA PROTEIN.	Q9GKV3	97% 27% 75%	1420 210 2701	2508 338 2823
HPJCL22	1034817	354	WUblastx .64	(Q9VWN8) CG7307 PROTEIN.	Q9VWN8	69% 61%	64 468	348 992
HPJCL22	1046434	355	WUblastx .64	(Q9H8F3) CDNA FLJ13680 FIS, CLONE PLACE2000007, HIGHLY SIMILAR TO HOM	Q9H8F3	94% 81%	346 16	582 162
HPMDK28	846357	199	WUblastx .64	(Q9NP77) CDNA FLJ10947 FIS, CLONE PLACE1000066, WEAKLY SIMILAR TO SSU	Q9NP77	100%	163	666
HPMDK28	639118	356	WUblastx .64	(Q9NP77) CDNA FLJ10947 FIS, CLONE PLACE1000066, WEAKLY SIMILAR TO SSU	Q9NP77	100%	157	660

HPRAL78	1352342	200	WUblastx .64	hypothetical protein DKFZp566D213.1 - human	pir T08724 T08724	99%	62	1312
HPRAL78	844216	357	WUblastx .64	(AAH08720) Unknown (protein for MGC:8447).	AAH08720	83%	70	1017
HPRAL78	484735	358	WUblastx .64	(Q91XD7) Unknown (protein for MGC:18896).	Q91XD7	51%	490	1068
HRABA80	882176	201	WUblastx .64	(Q9HA75) CDNA FLJ12122 FIS, CLONE MAMMA1000129.	Q9HA75	95%	124	336
HRABA80	588460	359	WUblastx .64	(Q9HA75) CDNA FLJ12122 FIS, CLONE MAMMA1000129.	Q9HA75	63%	647	679
HRACD15	871221	202	WUblastx .64	(AAH08084) Hypothetical 50.4 kDa protein.	AAH08084	48%	144	371
HRACD15	706332	360	WUblastx .64	(AAH08084) Hypothetical 50.4 kDa protein.	AAH08084	93%	247	507
HRACJ35	877666	203	WUblastx .64	(Q9Y5X6) BLOOD PLASMA GLUTAMATE CARBOXYPEPTIDASE PRECURSOR (EC 3.4.17	Q9Y5X6	63%	633	665
HRACJ35	730504	361	WUblastx .64	(Q9Y5X6) BLOOD PLASMA GLUTAMATE CARBOXYPEPTIDASE PRECURSOR (EC 3.4.17	Q9Y5X6	48%	130	357
HRACJ35	470546	362	WUblastx .64	(Q9Y646) AMINOPEPTIDASE.	Q9Y646	92%	233	493
HRGBL78	910133	204	HMMER	PFAM: Immunoglobulin	PF00047	98%	1452	253
						82%	1649	1581
						98%	1596	253
						98%	1468	1755
						99%	132	1472
						98%	1435	1722
						99%	99	1439
						96%	507	785
						100%	1	519
						32	582	755





				WUblastx .64	(Q9Y279) Z39IG PROTEIN PRECURSOR.	Q9Y279		88%	444	1040
HSDFJ26	834619	209		WUblastx .64	(Q9BYJ0) KSP37.	Q9BYJ0		99%	126	542
HSDFJ26	836071	370		WUblastx .64	(Q9BYJ0) KSP37.	Q9BYJ0		99%	99	767
HSJA15	795252	210		WUblastx .64	(Q9BZW5) TRANSMEMBRANE 6 SUPERFAMILY MEMBER 1.	Q9BZW5		100% 92%	99 238	281 768
HSAX21	612823	213		WUblastx .64	(Q9NV22) CDNA FLJ10983 FIS, CLONE PLACE1001781, WEAKLY SIMILAR TO PRO	Q9NV22		99%	5	598
HSIDJ81	589447	214		WUblastx .64	(Q9H728) CDNA: FLJ21463 FIS, CLONE COL04765.	Q9H728		74%	1289	996
HSJBQ79	1304677	215		WUblastx .64	(Q96D15) Hypothetical 37.5 kDa protein.	Q96D15		96%	38	586
HSJBQ79	661698	372		HMMER 2.1.1	PFAM: EF hand	PF00036		23.4	663	734
				WUblastx .64	(Q96D15) Hypothetical 37.5 kDa protein.	Q96D15		99%	54	1037
HSJBQ79	371784	373		WUblastx .64	(Q96D15) Hypothetical 37.5 kDa protein.	Q96D15		97%	32	586
HSKDA27	1352409	216		WUblastx .64	(BAB85613) URB.	BAB85613		83%	786	3635
HSKDA27	1074734	374		WUblastx .64	(BAB85613) URB.	BAB85613		60% 60%	1601 1715	1789 1789





HTEJN13	1352272	235	.64 WUblastx .64	adhesion molecule 2. (Q9BWWY1) BA552M11.5 (NOVEL PROTEIN) (FRAGMENT).	Q9BWWY1	100% 100%	158 351	193 779
HTEJN13	658744	384	.64 WUblastx .64	(Q9DAR9) 1700001D09RIK PROTEIN.	Q9DAR9	60% 77%	525 163	743 516
HTEJN13	381941	385	.64 WUblastx .64	(Q9HBK8) AD026.	Q9HBK8	92% 94%	191 214	229 633
HTPLP17	836072	236	.64 WUblastx .64	(AAH24188) Similar to RIKEN cDNA 4930453N24 gene.	AAH24188	100%	22	465
HTELS08	847090	237	.64 WUblastx .64	(Q9JI83) EPCS26 (PLAC1) (PLACENTAL SPECIFIC PROTEIN 1).	Q9JI83	34%	33	395
HTLEP53	634852	238	.64 WUblastx .64	(Q8WTZ3) Hypothetical 27.2 kDa protein.	Q8WTZ3	66% 68%	543 806	499 534
HTPCS72	854941	240	.64 WUblastx .64	(O95880) UNKNOWN.	O95880	100%	2191	2577
HTPCS72	566683	386	.64 WUblastx .64	(O95880) UNKNOWN.	O95880	100%	356	742
HTPIH83	919916	241	HMMER 2.1.1	PFAM: PMP- 22/EMP/MP20/Claudin family	PF00822	81.5	127	660
			.64 WUblastx .64	(P57739) CLAUDIN-2.	CLD2_HUMAN	100%	118	807
HTPIH83	895024	387	HMMER 2.1.1	PFAM: PMP- 22/EMP/MP20/Claudin family	PF00822	55.9	120	500
			.64 WUblastx .64	(P57739) CLAUDIN-2.	CLD2_HUMAN	98%	111	530

HTPIH83	898088	388	.64	(P57739) CLAUDIN-2.	CLD2_HUMAN	96%	96	353
HTTBS64	1008159	244	WUblastx .64	(O00172) LINE-1 REVERSE TRANSCRIPTASE (FRAGMENT).	O00172	50%	932	714
HTXAJ12	1310814	246	WUblastx .64	(Q9D7W4) 2210021G21RIK PROTEIN.	Q9D7W4	45% 57%	12 97	77 273
HTXAJ12	567434	391	WUblastx .64	(AAH24685) Similar to transmembrane 4 superfamily m	AAH24685	100% 98%	9 97	95 267
HTXJM03	603918	247	WUblastx .64	(Q9BRH0) SIMILAR TO DKFZP727C091 PROTEIN.	Q9BRH0	100% 99%	470 564	565 1760
HTXK95	891275	248	WUblastx .64	(AAH08360) Similar to hypothetical protein FLJ22376	AAH08360	84% 92%	324 81	644 203
HTXK95	834438	392	WUblastx .64	(AAH08360) Similar to hypothetical protein FLJ22376	AAH08360	100%	2	553
HTXON32	838288	249	WUblastx .64	(Q96NR6) CDNA FLJ30278 fis, clone BRACE2002755.	Q96NR6	58% 64%	1397 1194	1498 1397
HWAAD63	838626	252	HMMER 2.1.1	PFAM: Sodium/calcium exchanger protein	PF01699	62.8	346	453
			WUblastx .64	(Q9HC58) SODIUM/CALCIUM EXCHANGER NCKX3.	Q9HC58	65%	229	813

HWAAD63	833089	393	HMMER 2.1.1	PFAM: Sodium/calcium exchanger protein	PF01699	37.8	346	453
			WUblastx .64	(Q9HC58) SODIUM/CALCIUM EXCHANGER NCKX3.	Q9HC58	78% 55% 72%	229 429 533	453 596 814
HWAAD63	793875	394	HMMER 2.1.1	PFAM: Sodium/calcium exchanger protein	PF01699	113.7	336	773
			WUblastx .64	(Q9HC58) SODIUM/CALCIUM EXCHANGER NCKX3.	Q9HC58	76%	219	806
HWBCP79	846382	254	WUblastx .64	(Q96MM0) CDNA FLJ32172 fis, clone PLACE600055.	Q96MM0	27% 85%	340 158	143 78
HWBCP79	646977	395	WUblastx .64	(Q96MM0) CDNA FLJ32172 fis, clone PLACE600055.	Q96MM0	27% 85%	330 148	133 68
HWBEM18	949402	255	WUblastx .64	nuclear pore protein gp210 precursor - rat	pir S04921 S04921	84%	102	5735
HWBEM18	906580	396	WUblastx .64	nuclear pore protein gp210 precursor - rat	pir S04921 S04921	87% 30% 79%	92 2595 2626	2629 2732 3570
HWBEM18	877573	397	WUblastx .64	(BAB84927) FLJ00172 protein (Fragment).	BAB84927	99%	37	1494
HWBFX31	799427	256	WUblastx .64	(Q9N083) UNNAMED PORTEIN PRODUCT.	Q9N083	56%	1663	1517
HWHGZ51	886212	257	WUblastx .64	(Q9UJ74) HYPOTHETICAL 36.0 KDA PROTEIN (C4.4A PROTEIN).	Q9UJ74	100%	33	1070
HAGAI85	381942	259	WUblastx	(O15432) PROBABLE	COP2_HUMAN	100%	91	234

				.64	LOW-AFFINITY COPPER UPTAKE PROTEIN 2 (HCT		96%	228	518
HOFOC33	1186156	260	WUblastx .64	clusterin precursor - dog	pir A40018 A40018		69% 81%	1022 115	1414 1086
HOFOC33	967554	398	HMMER 2.1.1	PFAM: Clusterin	PF01093		236.4	81	395
			WUblastx .64	clusterin precursor - dog	pir A40018 A40018		44% 91%	373 81	453 395
HOFOC33	878690	399	HMMER 2.1.1	PFAM: Clusterin	PF01093		236.6	81	395
			WUblastx .64	clusterin precursor - dog	pir A40018 A40018		44% 91%	373 81	453 395
HOFOC33	905734	400	HMMER 2.1.1	PFAM: Clusterin	PF01093		301.2	76	432
			WUblastx .64	clusterin precursor - dog	pir A40018 A40018		77% 95% 86%	1023 76 440	1415 432 1087
HOFOC33	902326	401	WUblastx .64	clusterin precursor - dog	pir A40018 A40018		84%	583	257
HOFOC33	885140	402	WUblastx .64	clusterin precursor - dog	pir A40018 A40018		77%	839	36
HOFOC33	806819	403	HMMER 2.1.1	PFAM: 60s Acidic ribosomal protein	PF00428		74.6	-422	-733
			WUblastx .64	acidic ribosomal protein P0, cytosolic [validated] - human	pir A27125 R5HUP0		52% 87%	5 42	55 812
HSDEZ20	1352287	261	WUblastx .64	probable voltage-activated cation channel - rat	pir T17101 T17101		98%	4	336
HSDEZ20	704101	404	WUblastx	probable voltage-activated	pir T17101 T17101		89%	9	335





### ***RACE Protocol For Recovery of Full-Length Genes***

Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., Proc. Nat'l. Acad. Sci. USA, 85:8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start codon of translation, therefore. The following briefly describes a modification of this original 5' RACE procedure. Poly A<sup>+</sup> or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, SalI and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or SalI, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar methods known in the art and/or commercial kits are used to amplify and recover 3' ends.

Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-stranded cDNA), developed by Dumas et al., Nucleic Acids Res., 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to the first-strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is difficult to sequence past.

An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a

symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

***RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes***

Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3' RACE. While the full length gene may be present in the library and can be identified by probing, a useful method for generating the 5' or 3' end is to use the existing sequence information from the original cDNA to generate the missing information. A method similar to 5' RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript and a primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase if used is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant gene.

The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC (e.g., as described in columns 2 and 3 of Table 1A, and/or as set forth in Table 1B, Table 6, or Table 7) is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as described, for example, in Table 1A and Table 7. These deposits are referred to as "the deposits" herein. The tissues from which some of the clones were derived are listed in Table 7, and the vector in which the corresponding cDNA is contained is also indicated in Table 7. The deposited material includes cDNA clones corresponding to SEQ ID NO:X described,

for example, in Table 1A and/or Table 1B (ATCC Deposit No:Z). A clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X, may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Furthermore, although the sequence listing may in some instances list only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to sequence the DNA included in a clone contained in the ATCC Deposits by use of a sequence (or portion thereof) described in, for example Tables 1A and/or Table 1B or Table 2, by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 1A and Table 7 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59- (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the deposited clone (ATCC Deposit No:Z). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X or the complement thereof, polypeptides encoded by genes  
5 corresponding to SEQ ID NO:X or the complement thereof, and/or the cDNA contained in ATCC Deposit No:Z, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

10 The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

15 The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

20 The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in  
25 the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA sequence contained in ATCC Deposit No:Z. The present invention also provides a polypeptide comprising, or alternatively,  
30 consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or a complement thereof, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or the polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by  
35 SEQ ID NO:X, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C are also encompassed by the invention. The present invention further encompasses a

polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, a nucleic acid sequence encoding a polypeptide encoded by the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA contained in ATCC Deposit No:Z.

Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in Table 1C column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in Table 1C column 6, or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have

a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table 1C, column 1) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1C which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (See Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of Table 1C column 6, or any combination thereof.

Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1C column 6, or any combination thereof. In preferred embodiments, the polynucleotides of the invention comprise, or alternatively  
5 consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1C column 6, wherein sequentially delineated sequences in the table (i.e. corresponding to those exons located closest to each other) are directly contiguous in a 5' to 3' orientation. In further embodiments, above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the  
10 same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC  
15 ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and  
20 antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides encoded by  
25 these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1C which correspond to the same Clone ID (see Table  
30 1C, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, Table 1B, or Table 1C) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same Clone ID. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

35 In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence

of SEQ ID NO:X (e.g., as defined in Table 1A, Table 1B, or Table 1C) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same row of column 6 of Table 1C. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant



of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides, are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same Clone ID (see Table 1C, column 1) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one sequence in column 6 corresponding to the same contig sequence identifier SEQ ID NO:X (see Table 1C, column 2) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same row are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

**Table 3:** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. Accordingly, for each contig sequence (SEQ ID NO:X) listed in the fifth column of Table 1A and/or the fourth column of Table 1B, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. More specifically, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a and b are integers as defined in columns 4 and 5, respectively, of Table 3. In specific embodiments, the polynucleotides of the invention do not consist of at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. as disclosed in column 6 of Table 3 (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone). In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

Table 3

cDNA Clone ID	SEQ ID NO: X	Contig ID:	EST Disclaimer		Accession Numbers
			Range of a	Range of b	
H2CBU83	11	884134	1 - 2689	15 - 2703	BE613316, BE739453, AW961199, AV658769, BE785673, AW963999, BF037119, BG030580, BF036149, BF699154, BF033837, BF697524, BF695458, BF036638, BF701778, BG030507, AW377122, BF665913, BF699078, AW377125, BF665294, AV658829, BF667082, BG166746, AW851261, BF241480, AW850925, AI978869, BF695890, AA845339, BF668201, BF699860, BF085620, AA405940, BE612726, BF666583, BF667787, BE739116, BF665805, AW752845, BF701466, AI800939, BG121547, AI620357, BF700054, AW851052, AI924880, AW752835, AI800807, BF697582, BF700919, BF667321, AI139396, BE958619, AV692286, AI955392, AW752844, BE042841, BF698625, BF244588, AW440250, BF698345, AW152584, AW955901, AI671911, AA535832, AW850982, AI935579, BE089877, AW752868, AI683119, BF130660, D61864, AW630835, AI621153, BF514638, BF697211, AW192136, AI286255, AA403153, D62117, AW028833, N78154, BF154792, BF665821, AI538061, N64201, AW851056, AW938593, BE093579, AW938596, AA928873, AV651183, BE817020, AV657915, AV657131, BF666276, AV660141, AI699025, AI016115, R66206, N45586, D61708, BE868472, AA403241, AV657914, AA313513, AV682813, H88565, AA531589, R58698, AA857811, H42631, AA307010, R67084, BF334107, AW971385, R68027, AW021104, AW296538, BG166828, AI887214, AW468968, R64487, H88521, BF697149, R94825, R68028, R92884, R65584, AA377208, AI050980, AA318641, D62093, BF813323, N78160, T73957, D61982, D62303, D62026, AI806100, AA095925, N56560, T73925, AA507092, BF750358, BE148612, BF750357, BE867141, T73948, N88292, T73916, BE044052, H95089, H73281, AV660091, AF257182.1, AF346711.1.
H6EDC19	12	543259	1 - 746	15 - 760	AI090153, AI767722, BG116691, AI797075, BF528376, AI698172, AI681570, BE671343, AI539236, AV704244, AI539246, BE264613, AA864681, AW204700, AI808925, BE676036, T79284, BF445461, AA400027, AI209219, AA300244, AA427390, AA302217, AA252421, AA406631, AI869251, BF969629, AI262951, AI498669, AA300243, AW072158, T79197, AA411721, AV682333, F34003, AI123608.
HACBD91	13	637482	1 - 1431	15 - 1445	AI123694, AA203656, AV707802, BF575227, N77966, AW956121, N71852, BF732312, AI338999, AA704675, AI742966, AA176725, AV744696, AI039168, AA329423, AA680411, F10345, T85994, AV682639, AA731436, AV735262, AV733694, AA505796, AW959998, BF793146, H79631, R00088, BF978632, BG034327, AV716953, AW955313, BG032189, AV717860, AV716893, BF244606, AV733654, BG030662, AI802907, AA528524, AA973692, AA658895, AV714250, AV718258, AV716004, BF029739, F26324, AW772717, BE909294, AA370595, AI392630, BF529817, AI914394, BE748127, AA975366, BF029799, AI126532, AA977864, R38577, AI093884, AW264528, AI351443, AA916014, AA359165, AA594324, AI682171, AA404535, BG034254, T75123, AI832970, AA973611, AI833308, AI814033, BE781781, BF035996, BF036344, AA888167, BE541776, BF109665, BE551387,

					<p>AI268514, AV710503, AI709250, F33691, BF216659, F33502, BE467615, AV738506, BE503802, AV763934, BG110890, AV742881, AV710956, BF965198, BG033031, T90966, R02459, F32392, BF029956, BF690853, AV764373, BE738142, BF244383, AW772766, BF978393, BF030821, BE548289, N64163, BF576733, AW872492, BE218579, BE539011, BE042987, BF978138, BE217894, BF692527, AW419258, BF219313, BF244019, R02355, BF242775, AA340839, AW440167, F30529, BE748667, AA640120, BG179795, BF679132, BF382290, AI719390, R35603, BF240791, BF691038, AW009337, AA886535, BE738709, AI253328, AW268515, BF977850, H79632, AV764541, BF214426, BE184678, BE171856, BF382191, F12739, BF031722, BE564110, F21702, BF219100, F26311, F27624, F31646, F24066, F30253, F21442, BF030470, BF215493, AA365400, AV725369, BF243623, BF216495, F23622, R38445, Z20180, F23439, BF031636, AA340808, BF246303, F29361, BF212059, D19917, BF210763, AI720401, N58379, AA706899, BE737668, F37786, AC009289.8, BC000855.1, AF044957.1, AC008804. 6.</p>
HACCI17	14	891114	1 - 1708	15 - 1722	<p>AL538454, BF530920, BF530060, AI970528, AI860328, BF527064, AI798917, AL538453, BG054790, AI923543, BF219866, BF528175, AV752086, BF526803, AI800076, BF526264, AW206433, AI337330, AW245447, AW237083, BE858481, BE466614, BF437709, AI497639, AI160768, AW245805, AA131235, BE672804, AI160855, BF109500, AI675102, AI804002, BG060000, BF222422, AI982947, AI355974, AW590096, AI418181, AI312842, BF224013, AI088289, BG056127, AI332684, AI341205, AI654907, AI083806, AI798674, AI470925, AI190394, AW139187, AI092606, BF222526, AI291977, AI611140, AW135968, AW204680, BF106163, AW025331, AI167288, AI656880, BG058349, AA971379, AI399811, R72939, AA037774, AI150867, AI928634, AW302173, AI918209, AI350940, R73561, AA034204, BG152416, AI810527, AA621414, BF061361, AI783733, AI817644, H94482, R60154, T35689, BE504130, BF111371, BF725784, AI970869, BF056386, BF445420, AI925534, BF831443, AA885412, H49844, AW572977, BF939724, BF220095, R60153, F37217, BF525690, AI654502, AW189678, AA131356, BC002404.1, AF000959.1, AC000082.4, AC000071.2, AC000088.2, T69988, N39621, N46769, AA034265, AA918849, AA707092, AA758314, Z38200, AA772946, AI418724, AI420314, AI423722, AI423730.</p>
HAGAQ26	15	561996	1 - 1319	15 - 1333	<p>BF111995, BF111899, AW051348, AI807015, AA349378, AA349433, H05458, T39468, T39511, F02812, T50009, T50073, Z43427, AI372659, BE843943, BE843903, AA860404, BG015163, BE938621, BE843892, AI372657, BE698483, BF092079, BE301746, BG015653, AA496848, AL045349, BE047833, BE965724, BE965432, BE875407, BE964497, AW059713, AL037454, BE964512, AL119836, BE967307, AI918408, BG180506, BE964876, BF924856, AI683559, AW151136, BG107576, BE965067, AW268261, AI691088, AI798271, AV689111, BG253692, BE011885, AI868163, AI918634, AW084097, BE875022, BE879931, AI340603, AV728806, AL036652, BF814335, AI370392, BE963838, AV725920, AW021717, AW089036, BE877142, BE964795, AI469516, AI805638, AI925404, AA291456, AL040694, AI285439, AA888196, BE966404, BE965758, BE544111, BG180273, AI366968, AW022682, AV742698, AI560679, AI345608, BE967149, AI366959, AI473536, BG153056, BE964614, BE540578, AI349933, AI623736, AW020095, BF038804, BE908276, AV742475, AI345471, BE966787,</p>

				AI343091, AI345677, BE966011, BE965621, AI340519, AW162189, BF814357, AW198144, AI446809, AV717295, AV716613, AV682144, AI366992, AA806719, AV682099, BE964661, AA789133, BE963918, BE904051, AW023338, AV738730, BE873776, BG027082, BF032404, BG164035, BE613727, BG032219, AI863357, BF965884, AL048323, BG153050, AI636719, AV756658, AW827289, AL048340, BE879905, BG109270, AW020693, AI686576, AW858254, BE964073, AI470293, AW827290, AW058233, AL038605, BG107625, AI702527, BG260037, AW834325, BE047952, BF793031, AA643235, AI418254, AI623905, AI538764, AI524654, AI249946, BE964006, AA848053, AV733819, AA635382, H42825, AI929108, BF924884, BG029053, BE974031, AI473451, AV711509, BG252714, AL048644, BF868927, AL040241, BE883591, BF968622, AW068845, AI624293, BF813196, AW022494, BF340323, AL046463, AW020288, AI521596, AW021373, AW162194, BF915316, BF925370, BF886214, AI923989, BE965481, AI868204, AI242736, BE891942, BE735380, BF909758, AA579232, BG166687, AV715354, BE964767, AV756247, AV758825, BF814449, AL038445, BE965121, AW163834, BF343521, AW084056, BG032169, BE904851, BF868811, BG104782, AI537677, BG122101, AI628325, AI590645, BE875402, AW083804, AI561299, BE908335, AW059828, BF753056, AI559863, AV726125, BF750879, AW265004, F26535, AI583032, BF811808, AI366974, AI355765, BF822127, AI609593, AI887775, AI858865, AI500061, BG121959, AA572758, BF699668, AI348897, BE778024, BF814504, AI345224, AI357599, AV681949, T99953, AI589428, BG113851, BG110517, AL530922, AF169301.1, AC091736.1, AL442082.1, AB049853.1, AL389935.1, BC007364.1, S78214.1, X99717.1, AL122121.1, AK027161.1, BC006195.1, BC001418.2, BC005858.1, AK000310.1, S77771.1, AL389939.1, AF090900.1, AF090934.1, BC003104.1, AK025092.1, AK024524.1, AB047897.1, BC007674.1, AB044547.1, AL136789.1, BC004874.1, AL122045.1, AK026506.1, AL389978.1, AL049464.1, AF067420.1, BC007355.1, M86826.1, AB063071.1, AL110196.1, BC001293.1, BC007998.1, BC006287.1, AL096751.1, AL133565.1, AF057300.1, AF057299.1, Y10080.1, BC008387.1, AK026518.1, AL133081.1, AL162006.1, U42031.1, AK027142.1, U51587.1, AF177336.1, AK000137.1, AL157479.1, AL137547.1, AL133093.1, AB063008.1, AK025431.1, AL390167.1, BC008673.1, BC000317.1, AB047869.1, AF205861.1, BC003650.1, AL133560.1, AK024538.1, BC000799.1, AK026480.1, AF218014.1, AL049382.1, AK027182.1, AK000421.1, AK000323.1, S76508.1, BC001774.1, AB051158.1, AB047615.1, AL137523.1, AL353957.1, U58996.2, AB055303.1, Z37987.1, AB060887.1, AK026452.1, BC008025.1, AL050170.1, BC003687.1, AK026395.1, AB060912.1, AL122111.1, AB060863.1, BC005160.1, AB056809.1, AB052191.1, Y14314.1, AK026927.1, AL096744.1, AL137658.1, AL137705.1, AL137292.1, BC000778.1, BC008185.1, S61953.1, AL137283.1, AF097996.1, AL049430.1, AL390154.1, BC006164.1, AL512718.1, AL049314.1, J05032.1, AL117583.1, AB063046.1, AF10640.1, BC001349.1, AF120268.1, AK000212.1, AK000083.1, BC006180.1, AK027164.1, AB047801.1, BC007534.1, BC000556.1, BC004905.1, AL110224.1, BC007021.1, AK026462.1, AL356278.8, AF162270.1, AL050277.1, BC008070.1, AL512684.1, AB047966.1, BC0006408.1, AF225424.1, AK000655.1, AB060856.1,

HAGFI62	17	704425	1 - 989	15 - 1003	<p>AK025573.1, BC001056.1, AB047631.1, BC005890.1, AL137273.1, BC004370.1, AF207829.1, BC002491.1, D83989.1, BC004943.1, AF239683.1, BC005007.1, AF111112.1, AL122049.1, BC009033.1, L19437.2, AK026086.1, AB060883.1, AK026045.1, AB056420.1, AF305835.1, AB060903.1, AK026434.1, AL133568.1, AL122118.1, AL050393.1, AL137476.1, AC023880.5, AL117435.1, AK026534.1, BC000348.1, BC005678.1, AJ001838.1, S78453.1, AL136767.1, X76228.1, M64349.1, BC005151.1, AB055370.1, AB060893.1, BC001963.1, AF159615.1, AK026603.1, AL512689.1, AL133075.1, BC007680.1, AL136754.1, AK025708.1, AL050146.1, AF217991.1, AL117440.1, BC007897.1, AL136766.1, AL117629.1, BC006133.1, AK000450.1, AK026592.1, AF003737.1, AL050024.1, X69819.1, AB049900.1, AK025958.1, AK025084.1, L30117.1, AL080074.1, AB048974.1, AB063084.1, BC002471.1, BC006411.1, AK025772.1, AF090896.1, AL137488.1, BC000066.1, AK026551.1, U77594.1, BC002777.1, AL353802.14, AF271350.1, BC000632.1, AK026533.1, BC009026.1, BC003683.1, AK027096.1, AK025414.1, AB050411.1, AK027104.1, AK026353.1, BC002541.1, BC004297.1, U39656.1, AK026522.1, AB050534.1, AL136644.1, BC006440.1, AK026885.1, AK026571.1, BC003682.1, AK025541.1, AL136843.1, BC004431.1, AF132730.1, AF219137.1, AL137574.1, AF090886.1, AL136893.1, AK024944.1, AK025015.1, AL050116.1.</p> <p>AI693333, AA774471, H49659, AA009946, AW664812, AI217416, R56893, T88930, H44134, R67277, F10016, R52911, R39072, D61015, AI972242, Z44064, BF790840, AI090826, F06072, Z38995, R35532, AF131817.1, AF198490.1, AF181450.3.</p>
HAHDB16	18	635412	1 - 782	15 - 796	<p>AI688902, AI983921, AA843874, AA745961, AU150602, BG169215, AW571697, AA581433, AI685116, AW190486, AA152091, AI927861, BG059728, AI811494, AW089655, AI924175, AU118990, AI872415, AI858607, AI610776, BE044603, H97952, AF063514, AL137994, AV719347, AA189081, AW177120, AL133942, AW090739, AA767353, AW167319, AU145663, AA724159, AA493998, AA773359, AI367384, W49501, AI925647, AI334099, AA631430, AU143906, AI874256, AI264673, AI887321, AA160519, AL119355, BE646447, AW468887, AI749571, AW177226, AI761656, BF882284, AI801377, AW177317, AV726924, AU121759, AL036881, AI082077, AW177231, AI088796, AI675848, T16214, AI818151, AI627862, AW994225, AW084901, AW177264, AI250812, AU157470, AV730063, N64574, AI625127, BF056069, AW073349, AI735074, AI590151, N24958, AW813744, AI963795, N76274, AI732743, AI560839, AA174085, C06012, AA085707, AI811854, AA601264, W03759, AW090210, T69719, AW177237, AV699636, AI570877, BF823687, AI418614, BE379085, AA152017, BF436023, AA953572, AI433018, H91008, BF930080, AA709024, N79242, AU145674, H64113, AV720543, AI346802, AI568919, AU146451, AA287329, AW242205, H90881, AW242735, AA778304, AI034217, AU145383, AW589529, AI628043, AI027421, AW235478, AI860964, AI499811, AU146974, BE148908, AI375534, AA946637, AA807609, AW157413, AI683685, BF760502, AW589501, W87732, AA524883, W58442, AA678653, AI591192, AI189033, BF439824, AA470572, AA136637, M62281, AI632138, R48563, BE247178, AI272961, AI376984, AI524521, AI197934, AI025602, AW874038, AU143935, BG235936, AU144339, AI955464, AA782144, R80440,</p>

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HAICP19	19	422672	1 - 1610	15 - 1624	AL354857.13, AL359438.19, AC012603.6, AL049834.3, AL121995.12, AL360219.18, AL589946.4, AL391379.12, AC011998.8, AC024095.13, AL442203.12, AL354858.16, AC022081.32, AC073148.7, AL450347.5, AC002556.1, AL158016.15, AL121782.9, AC005406.2, AC073273.9, AL445493.8, AP001831.4, AC012653. 8. AL533390, AL529681, AL528191, BF966576, AL523718, AL528190, BG120879, BF115284, AL529855, BE785817, BF026199, BF966448, BG114227, BE386416, BF115429, BF304689, BF304827, BE728367, BE793198, AV704155, AL529854, BE260405, BF305469, BE789342, BE297311, AW993505, BF316927, AW993825, BE277343, AW993830, BE265484, BF727063, AW960096, BF831956, A1743647, AW965178, C17555, BF838669, A1923650, A1860279, BF057404, AW005358, A1146421, BF928251, A1093908, BF747949, BE047374, BE813316, A1769656, AA605064, A1241016, A1148817, A1318082, W31773, AA565734, A1630731, AA843395, AW025017, A1566682, BF955698, AA506224, AA749014, AA827318, AW134754, N31961, BE774133, F36487, AA346026, T49220, AV750102, W04672, F31348, N31991, A1827206, A1630730, T49219, BF990595, A1678457, AA879426, A1120831, AA948142, AA345290, A1685001, BG007518, BG011225, AA120830, BE774243, BG004311, BE073338, BF155353, T39496, BE774391, BG007508, AW374473, AJ299442. 1. BE262907, AW503376, AW503644, BF982382, BE079288, AW504239, AA701415, BF315343, BE277664, BF921555, BF736464, BF756620, BE720223, BE815902, AA490675, BE930704, AW971745, AW804686, AW392670, BE695785, AW861944, AW604723, AW877209, AL119483, U46351, AW858526, AW858525, AL042984, AL119497, AL119324, AL119319, AL119355, AW500561, U46349, AL134538, AL119457, BE705903, BE705906, AW577135, AW372827, AW384394, AW861889, AW858455, AW363220, U46350, Z99396, AL119484, AL119363, AL119391, U46347, U46341, AL119443, BF868687, AL119444, AL119341, BF868697, AW604726, AL119439, BF868684, BE705905, AL119522, AL119396, U46346, AL119335, AL134531, AL134533, AL037205, AL134920, AL134525, BE705904, AL119399, AL043029, AL119496, AL119418, AW861954, U46345, AL043011, AL042614, AL042975, AL043033, AL042544, AL042965, AL134542, AL042450, AL042542, AL043019, AL043003, AL119464, AL042551, AB028986.1, AB026436. 1. AL530791, AL530792, AL529741, AL535065, AL535066, AU124538, AU133125, BG248951, BG170992, BF342607, BE791618, BE788808, BE889885, BE899228, BE266316, BF666992, AA604226, BE855814, AA858439, BF306389, AW965351, A1459262, A1949460, BE566846, A1920795, BF695661, A1628581, A1810626, AA213464, BF436958, A1765166, BF131526, AA446901, BE669483, BF105045, AA165298, AW300022, N48825, AA595754, BE218460, BF126313, AA165297, BE044264, A1686706, AW300346, BF760498, A1472286, A1804402, AA426331, A1278834, AW169453, AW239143, AA426332, H29503, AW602873, AA213575, BF376918, AV749783, AA075971, AA447021, AA074072, BE244841, A1002939, BE832901, AA598694, BE694349, A1471852, A1961851, AW136228, A1422999, AA707156, H29787, AV692260, AV692283, AV692263, BE243932, BE244952, BF330518, AV698872, AA333388, AV698900, AV691373, AV695584, AV694677, AV687965, AV696854, R13303, AA564851, A1762353, BF751566, BE244135, AV690233, AV696838, BE463584, T05291, BF878149,
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HAMFE15	23	905695	1 - 4115	15 - 4129	BE262907, AW503376, AW503644, BF982382, BE079288, AW504239, AA701415, BF315343, BE277664, BF921555, BF736464, BF756620, BE720223, BE815902, AA490675, BE930704, AW971745, AW804686, AW392670, BE695785, AW861944, AW604723, AW877209, AL119483, U46351, AW858526, AW858525, AL042984, AL119497, AL119324, AL119319, AL119355, AW500561, U46349, AL134538, AL119457, BE705903, BE705906, AW577135, AW372827, AW384394, AW861889, AW858455, AW363220, U46350, Z99396, AL119484, AL119363, AL119391, U46347, U46341, AL119443, BF868687, AL119444, AL119341, BF868697, AW604726, AL119439, BF868684, BE705905, AL119522, AL119396, U46346, AL119335, AL134531, AL134533, AL037205, AL134920, AL134525, BE705904, AL119399, AL043029, AL119496, AL119418, AW861954, U46345, AL043011, AL042614, AL042975, AL043033, AL042544, AL042965, AL134542, AL042450, AL042542, AL043019, AL043003, AL119464, AL042551, AB028986.1, AB026436. 1. AL530791, AL530792, AL529741, AL535065, AL535066, AU124538, AU133125, BG248951, BG170992, BF342607, BE791618, BE788808, BE889885, BE899228, BE266316, BF666992, AA604226, BE855814, AA858439, BF306389, AW965351, A1459262, A1949460, BE566846, A1920795, BF695661, A1628581, A1810626, AA213464, BF436958, A1765166, BF131526, AA446901, BE669483, BF105045, AA165298, AW300022, N48825, AA595754, BE218460, BF126313, AA165297, BE044264, A1686706, AW300346, BF760498, A1472286, A1804402, AA426331, A1278834, AW169453, AW239143, AA426332, H29503, AW602873, AA213575, BF376918, AV749783, AA075971, AA447021, AA074072, BE244841, A1002939, BE832901, AA598694, BE694349, A1471852, A1961851, AW136228, A1422999, AA707156, H29787, AV692260, AV692283, AV692263, BE243932, BE244952, BF330518, AV698872, AA333388, AV698900, AV691373, AV695584, AV694677, AV687965, AV696854, R13303, AA564851, A1762353, BF751566, BE244135, AV690233, AV696838, BE463584, T05291, BF878149,



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HAMGR28	24	892971	1 - 1660	15 - 1674	AL519641, AL519640, AL525613, AL526308, AL527643, AL530324, AL525663, AL525671, AL530325, AL515833, AL515832, BF313053, AL527577, BF529163, BE312001, BF984557, BF530620, BE396752, BE304484, BF983145, BE560368, BF316599, BG114646, BE269376, BF313413, BE298748, BE440179, AW953553, BF307907, AW978612, BE617303, AA845426, AI830874, AI983227, AW956917, AW410199, AW628335, BE464326, AA530876, AW452186, BE139083, AI829507, AI356849, W69111, AW084551, AA406233, AI589504, AI970964, AI420766, AI701901, AI130010, AI288363, BF571959, AI683363, BE019516, BE206283, AW272707, N23238, AA593625, AI000296, AA406505, AW593667, AI933020, AI337797, BF691989, AI139514, BF062876, W35301, AI418519, AV759081, AW514035, AW004995, AW591716, F28754, AA815275, AI347528, AI624104, AA574436, AI817434, AI025110, T08849, AL527576, AI079740, AA962799, AA707405, BF445536, F37186, AW207522, AW591663, AW263070, AW510310, AW264517, AA028008, T33149, AA723895, W69236, R40168, T23442, H88132, H78378, AW514039, D12424, W23701, F34521, Z43089, BE646197, AI475064, AA653748, AA312858, AW959275, AW410198, AI932423, AA121114, AA121036, AA295884, AA356831, AI310743, BF513002, AA381766, Z39180, RI2971, AW379122, AI768799, BE877018, AI560685, AA338084, AI810799, AW861944, AW750703, F24446, AW972092, AW858525, AW877209, AW968355, AW968356, AW972093, AW968729, AW971740, AW972091, AI431351, AW972090, AW969229, AW858455, AW804686, AL119324, AI432644, AI623302, AW604723, AW858526, AI432647, AI432653, AW081103, AI432661, AI492519, BE672748, BC007438.1, AC004150.8, AF064854.1, AB026436. 1.
HAPBS03	25	656755	1 - 1489	15 - 1503	AI742631, AU119590, AU118010, BG259904, AI800165, AI800177, AI817228, BG180146, BE813479, BE535299, AV725950, AW009788, BE549267, BE894325, AV757104, AA173790, BF038610, AU150757, AI983626, AU144839, AI580092, AA479607, AU145896, N31934, AU144384, W72461, AU152288, AI826420, AI817464, AU150963, AU151993, BE780217, AU145816, AU160659, BF817682, AA486402, AU150397, AW272227, BE813518, BE280368, AI400650, AI829127, AI859821, BE902423, BE349331, BF326757, AU145027, BE813644, AU156304, AU149695, BE902011, BE731981, AI200823, BG060141, AU135928, AA812768, AW162031, AI804420, AU148793, BE350105, AI810286, AI174621, AU160342, BE731153, AU156374, AV706272, AA262076, AV701945, AW768265, AI436131, AW204987, AW104123, BE218179, AU153197, BF970278, BF570446, AI092268, AA191221, W76519, AW630344, BF973324, BE548188, AW628275, AU157431, AI830727, BE045222, AW474225, BE536210, BE927040, AW204297, AI095806, BF229981, AW075962, AA279162, AI419217, BE504508, AW571815, BG059854, AW054950, AU143588, AA132187, AA346081, AW272217, AA937599, AA768309, BG119737, AI269189, AA213390, AW470843, BG152444, AA345939, AU119495, AW472911, N79590, BF965572, BE927026,

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HATBR65	29	635514	1 - 798	15 - 812	BF032466, BF342490, AI540614, BE264109, BE926389, BF309156, AA232553, BG255921, BE392626, BE261742, AI085402, BE206819, BE276164, BF312350, BF206486, BF763257, BG252820, AA642901, AW188803, AI758262, AA908888, BF207123, AW137361, BE258582, BE384894, AI093805, BG257985, AI751518, BF810986, BF337632, BF796886, BE397750, BE504399, F19099, AA610640, BF794720, BG104721, AI581186, BC002494.1, AC004150. 8. AW754098, AV747079, AW964560, BF827304, AI697254, AA826321, AA663880, BF924786, AA772037, AV725414, AA826164, AA663006, AA826322, BE062047, AA835931, AA319870, R95053, AV760830, BF918713, BF959165, AI053538, BF930635, BE828744, AA078591, AF139781, AA491430, AA078183, AW393403, W74390, AW578861, AW393400, AA320812, BF840307, AA078213, AW752269, BF757569, AA077448, BG004304, AW793003, AA047825, AA001509, AA076683, AW857010, BE183669, BE183617, BE699552, AV720211, AW973541, BE932909, AI254770, AI284543, AI251203, AI249853, AV743864, AI251284, AW276678, AW966385, BF952670, BE707812, AI251034, AI250552, AW970571, AW869794, BE139139, AA609826, AW303098, AA552586, BF952311, AV719632, AV718487, AW905386, BE138387, AV720104, BF952747, AA015737, AW975623, BF129140, AA076784, AA604865, BG222875, AV720729, AA504818, AW905269, AV754716, AW969831, AA501867, BE042006, BF589824, W72324, BF691892, AI954192, AA610381, AA503018, AA747757, H04977, AA904211, AI912401, AI279417, BE968744, AC004084.1, AF030453.1, AC005088.2, AC004951.5, AC018720.5, AC007078.3, AC004980.4, AC007000.2, AC006480.3, AC004878.2, AC006014.2, AC007003.4, AC005488.2, AC005098.2, AC004867.5, AC004166.12, AK021477.1, AC005071.2, AC005236.4, AP000350.1, Z95115.1, AC073462.8, AC007792.1, X51956.1, Z95331.2, AC022382.3, AC087071.2, AC005291.1, AL035495.13, AL162424.20, AC002107.1, AC002106.1, Z98884.11, AF168787.1, AL157791.4, Z82215.1, AF172081.1, AC008116.8, AL008729.1, AC018809.4, AC079141.7, AC011811.42, AC006111.3, AC020558.4, AC007766.1, AL162426.20, AL139317.5, AL390838.26, AL031005.1, AL161779.32, AC004477.1, AC008392.6, AL162615.13, AC009509.7, AC003690.1, U95740.1, AL034372.33, AF196970.1, AF253417.1, AC000062.1, AL109825.23, AC024028.10, AL034553.12, AC003030.1, AL591398.2, AC005899.1, AL034400.2, AC073492.18, AC011473.4, AC005772.1, AL139316.5, AC006487.8, AC011472.7, AP001929.4, AP000963.2, AC072061.8, Z98051.6, AC005327.1, AC007225.2, AL109804.41, AC006057.5, AP001711.1, AL136984.20, AC009506.5, AL139100.9, AC008397.7, AC007199.1, AL137162.25, AF190464.1, AC009247.12, AC025430.5, AC005261.1, AC006357.5, AC005325.1, AL121880.21, AC008395.6, AP000314.1, AL353715.21, AC025166.7, AL049779.6, AL355336.15, AC011479.6, AC011495.6, AL359644.10, AC020904.6, AC004706.1, Z98044.13, AL049874.3, AC007201.1, AL161757.4, AC007130.2, AL139415.10, AC022384.4, AC008738.6, Z95114.19, AC090841.1, AC005378.2, AC022001.3, AL031848.11, AC018494.6, AL445435.11, AC002128.1, AC018811.4, AC007685.2, AL121601.13, AC004805.1, AL353777.18, AL359397.3, AC078818.19, AC007679.4, AP001781.4, AP000563.1, AP000194.1, AC007956.5, AC020633.3,
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HAUAI83	30	639009	1 - 896	15 - 910	BE439675, BF984328, BF978147, AW955502, BF337207, BE272543, AV757236, BE903592, BF212880, AW405217, BE743902, AI991315, AV701663, BE270100, BF681301, BG178791, BE222645, BG167626, BF132414, AW069149, BF238307, AV736544, BG255905, BF698492, BF130460, BF102497, AV745093, BE543668, AI93727, BE254068, AA934591, N24442, AI147316, BF680700, AV705947, BE734398, BG231583, BE256074, AV754408, AW014782, AI198642, BE646408, AA889969, AI709288, AW135010, AA877730, AI720901, AA496681, AA995328, AI032868, AW579254, AI186312, AI969715, AI660672, N23673, AA420567, AA427691, AI188938, AA471213, BG117664, BF102532, AI191317, AI325586, AI219152, AW000829, AI470155, AA843102, AI125390, BE312355, AW182893, AI141484, H93124, AW000718, AI268069, AA815421, AA708211, AA129884, AI023128, AI147588, AV724436, AA159902, AI129253, AA290635, AV706639, AI127280, N58266, AA315771, AI673417, AI587141, AI186000, AI142324, AI128437, AA723220, AI335350, BF687940, AA552070, AI087415, AA995933, AW300769, AA862543, AW008043, R68241, BE349483, AI241459, AI355685, AW304225, AW083014, AI277068, AI038096, AI160884, AA774420, BE407927, AA810159, W37128, W04866, AI828898, AI093015, AA732834, AV707544, AI934627, AA026633, W01678, H84951, AI279658, BF665006, AA419151, AA844949, AI096712, N71609, AV735174, N69652, AA159798, AI969153, AV729015, AA149944, N95063, AI798245, AV736793, AA771923, H20023, R99610, H50207, AA653091, N70496, AW104010, H40779, N33986, D55334, AV743438, AW130386, BF977248, AI125700, BE091971, AA572869, W00449, AI744165, AA157561, AA531221, AI275921, AA969778, H95780, N92248, AI159958, N38815, H20143, AI680770, AA305332, N77862, AV738026, N72206, AA037790, AI752109, AV743648, AA937128, AA962124, AA478395, AV741494, AV740102, H19070, R71518, H18782, R94908, BE621803, R77435, H99652, AA694460, AA641831, H21165, AW511932, AI184349, W38900, AA844297, H46188, W58208, W40195, R71470, N94261, T31343, BE620993, R70469, BE909620, N25251, AI752110, AV741554, AA165011, AA037789, H01343, AA643896, R77524, H23656, R70556, T30654, W37143, AA326924, C01763, R91937,

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HIBAMB15	31	671835	1 - 807	15 - 821	W27833, AI860764, AA809619, BF432929, AA768248, AI370876, AV748724, AI291737, H96013, AW051697, AI633038, AI784315, BE546233, BF980899, BF977483, AI138479.4, AI132855.4, AI121755. 23.
HIBGNUM56	33	1352412	1 - 850	15 - 864	AW954217, BE875979, BG025158, BF529722, BE395207, BE734057, BE789549, BE873075, BE785505, BE614806, BE738333, BE614883, BE253565, BF340317, BF737302, AA044211, BF792671, AW796084, AW238972, BF738993, BG012029, BF812968, BE876237, AW406916, BF901660, AI342703, AA075901, H25630, BE810793, BE183450, H43485, AA296837, R95168, BF809994, BF868942, AL532494, W95348, H80718, BF804848, AA287470, AA806231, AL532493, AA298795, BF997411, AA296696, AA296826, BF082160, AA218811, AA296869, BF331433, BF829581, AA034079, AV743953, AW802996, H73675, R55519, BE140100, BF056207, AI819836, BE737872, BF446055, AA465105, BE396147, AA044081, AA583464, AI582284, AA983595, BE775061, C00212, BF771777, BF799156, BF895320, BF931829, AI537196, BF771828, AA523623, R39644, AI521467, AI952620, BE828356, AA187096, H42497, AA297863, BF763569, AW338141, BF736987, BF248485, AI346295, AI424071, AW512207, BF905334, AI066489, AI028038, AA699982, N86960, AI358167, T10507, AI683820, BF245896, BE904822, BF978464, BF811185, AA622655, BF814100, AA304509, AA595646, AA912088, AA287334, AA643965, BF747982, W95391, BE043918, BF807379, AI279829, AA722634, AI817892, AA187305, H80719, AA485829, R55520, BE671577, BF750444, AI637718, BF674579, AA873526, AW103333, AI650465, AA531049, AA658172, BG057590, AA583458, AV743642, AV739884, AV742260, AV743114, AV738121, AV736224, AV744272, AV741543, AV738375, AV738262, AV743004, AV739415, AV736083, AV737550, AV737002, AV741197, AV737715, AV742899, AV741000, AL037348, AV737101, AV739156, AV739895, AV701296, AV743288, AV740805, AV740787, AV737726, AV737727, AV744332, AV739871, AV740443, AV742357, AV743197, AC002390.1, AFI77940.1, AL080096. 1.
HBIAE26	34	514418	1 - 1024	15 - 1038	AW237905, AI635440, AL079734, AV729929, H73550, AI669421, BE092488, AC004076.1, AY030284.1, AL139353.3, AC008569.6, AC011479.6, AL031659.9, AC083865.2, AL353807.18, AE006464.1, AL136979.16, AL163032.3, AC019097.5, AC015651.18, Z93023.1, AC011484.4, AC013449.8, AC005015.2, AC006120.1, AC084865.2, AC022116.5, AL512449.6, AL109797.18, AC005736.1, AC006008.2, AL022336.1, AC006329.5, AC002302.1, AL357515.26, AL035669.43, AF288742.1, AC005522.2, AC005840.2, AC021016.4, AC078962.30, AP002851.2, AL138787.11, AP001695.1, AL160269.14, AC005512.1, AL034420.16, AL354932.26, AC005088.2, AC011500.7, AC008666.5, AC010404.5, AC000353.27, AC011469.6,

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HBINS58	35	1352386	1 - 829	15 - 843	AI827239, AW104045, AL536345, AL096774. 9.
HBJFU48	36	460392	1 - 835	15 - 849	BF674706, AA657543, AV757289, BE139139, AI250552, AI251284, AI251203, AI284543, AI251034, AW674277, AI254770, AW303098, AA582073, AI249853, AC005696.1, AF045555.1, AC090514.1, AF243527.1, AP001725.1, U91318.1, AL121897.32, AP003357.2, AC008155.9, AC005081.3, AL132838.4, AC011470.5, AP000692.1, AL132640.4, AL109976.23, AL121992.24, AL135928.6, AL033529.25, AL353807.18, AC020916.7, AL138849.12, AC011247.10, AL158830.17, AP000501.1, AL008637.1, AC006270.1, AC011464.5, U95742.1, AC022384.4, AC011555.5, AL049795.20, AL033383.26, AC005921.3, AC012170.6, AC004922.2, AC007934.7, AC018828.3, AL121653.2, Z82215.1, AC022383.3, AL049636.22, AC007216.2, AC005971.5, AC005058.1, AC010431.7, AL135783.6, AC044797.5, AP000355.1, AL121928.13, AE006462.1, AL590682.9, AL451083.5, AL162724.16, AC004906.3, AC006312.8, AL359272.9, AP001666.1, AP001716.1, AF111169. 2.
HBJLC01	37	638410	1 - 858	15 - 872	AW962384, AW956292, AA631830, AV708590, AW964544, AV709418, AI814702, AV729132, AV726091, AA652816, AV657453, AW956077, AW962908, AW966634, AW963349, AV708167, AV703597, AV727065, AV703388, AV703232, AW961593, AV702425, AW961606, AW950632, AW963756, AW963609, AV701873, AW959734, AW962444, AV707331, AI525316, AV703761, AV729517, AV726754, AV707276, AW961313, AW963348, AV705525, AW962942, AW963583, AW966270, AV708720, H60864, AW950748, AC004033.3, AC007050.25, AC008745.6, AC005500.2, AP000502.1, Z94801.1, AF019413.1, AC005261.1, AC005332.1, AC025588.1, AC006372.2, AC008265.15, AL590763.1, AL359235.3, AP000789.4, AC005476.4, AC079602.15, AC009789.21, AC018638.5, AC024952.4, AL022318. 2.
HBNAW17	38	526797	1 - 587	15 - 601	AA713518, AA807610, AW104604, AA830415, AW975518, AL138824. 19.

HCE2F54	39	634016	1 - 1262	15 - 1276	AL530657, AL534642, AL519887, AL519439, BE257752, AA769913, AI609266, BE674973, AI652143, BG057242, BE046399, AI669608, AU157638, BF347064, BE046435, AI571552, AA406626, AI634414, AW731848, BE245626, AI372990, AW473891, AU153165, AA969877, AI458122, AA402109, AU157487, AI815017, AA936365, AA481847, AI052565, AA704608, AI860561, BE736308, AI591232, AA425187, BF685966, AA479747, AI922541, AA889587, AA992245, R47377, AV694506, AA707462, AA283778, BF589042, AI767815, AW439290, AI354234, AW630387, R82068, BF829195, BG152634, AA229272, BE246763, AI745410, AW074728, AI867440, AA405028, AI652744, AI799388, AW732540, AA724063, AI249812, R43967, BE247615, AA229721, AA290883, AA477093, BF847615, AW117313, AA425298, AW804421, AV661367, AW627358, AA456146, W45494, R82878, R82020, F35061, H01485, AW014040, F25139, AA339640, AI961334, AA478233, AA362857, AA326205, BE244646, AA229827, AA377429, AI186501, BG008599, BE242784, T32225, AV686564, AA688260, AI085847, AV686569, BE157547, AA860204, R08559, F09429, AA405272, BF845336, BF380796, BF380795, AI860044, AA883556, AA032260, AA332516, AA402982, AA332325, BE157532, AA336006, Z39018, AI695855, AI589935, AI583010, AI954634, BF841145, AW469249, F04759, AA032193, F04962, AI524382, BF922668, BE157535, H01586, AI298047, T89862, AL530658, BF883965, BF374266, M78413, BF883968, AW197535, AW952615, BF847600, AW007397, BE157466, AI907687, AI632570, AL519888, AK023173.1, BC007642.1, BC007864.1.
HCE3G69	40	728432	1 - 2070	15 - 2084	BE740754, BF339727, BE740538, BE277589, BE382940, BE618822, BE793142, BE390135, BF530091, AW969581, BF315345, BF340007, BG164152, BE618316, BE277504, BE740158, BE542020, BF527796, BF796337, BF310510, BE409091, BE545069, BE312476, AI979049, BF314374, AI828148, BF528364, BF341988, AA987262, AA789210, BE783336, AA552222, BE042994, BE408361, AA542834, BE262213, BF724352, BG170449, AA399248, AI399975, AA682879, AA709002, AA628073, AA523036, AI281261, AI749652, AI148325, BE297932, AI347619, AI206709, AI857651, AI304965, R77325, AI523697, AA349818, TI6002, H56978, N95160, AA351179, BF736456, BF919187, W16789, R61061, AA994296, BE872104, AW131936, T77786, BF805555, R42239, AI001897, R49103, H27917, AI216183, BF435415, AA349337, AA293132, AA349338, H47705, BF690107, BE909738, BE831416, T87999, R77274, AA017080, AA293765, H47615, W21536, R64334, H56891, BF813356, BF957635, BE827070, AI560786, R64335, T77787, AW380761, AI027520, AW380835, AI870267, AI263580, BE563729, AA324593, AA588228, AW955408, AI277032, R18259, AI566653, T33783, AW883586, D53543, BG105324, AW452975, R60940, H41337, R36021, T32921, BF895461, AI360103, AW380828, BE256741, AA057061, AI564056, AW327298, AI244916, W35216, BE262875, AL040896, BE501695, BE351024, BF058407, BE263311, T15786, AA812926, AA830661, BE693588, AI797886, BF314562, AA299346, AW451523, BF337822, AI520932, D80870, AA33807, AA058540, AW363994, AW604788, AW820702, AW820474, BF848412, BF312802, BE171868, AW604793, AW273608, AA610114, AA865732, AW363958, AA524542, AI089686, AA359625, W23626, D20577, AI150519, W31778, AI150517, AW997867, AV704757, AV706824, AV705873, BC002420.1, AL136758.1.
HCE5F43	41	612796	1 - 1751	15 - 1765	AL525531, BG034956, BE858832, BE897817, BF510434, BG253874, AI656560, AI628821, BF215392,



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HCEFB80	42	1143407	1 - 2480	15 - 2494	BF343021, BF339312, BF341481, BF967606, BF344530, BF344213, BF513319, AI393526, BE857064, AW016800, AI937454, AI370995, AW170034, AA416907, AW044650, N75664, BF341415, AW960857, BG222497, AA703765, BE855450, AU146334, AA703342, N64813, T23840, AA446784, AA228781, M86149, T08275, AA386225, AA417008, AI671567, T15689, AW128975, AA432098, H83023, M85314, AI277779, BG222958, BF923571, M79106, BG152559, R13095, R11764, R21361, BF921573, F05369, T28040, T10247, AA323697, AI361427, AW235399, AI352392, T10246, R37689, AW594074, R40527, H82804, N59328, BF894586, R46460, T15861, BE672078, C14288, D25217.2, AF319633.1, AL022327.17.
HCENK38	43	658737	1 - 1495	15 - 1509	BG178033, BE896063, AV722833, BE907276, BE277857, BF952019, AA521308, AW182868, AA908959, AI628880, AW173363, AW665845, BE870003, AW631238, AI151418, BF996707, AI818267, BG180581, AI653663, AA001203, BE150445, R78710, AA130178, W03542, AA746655, AI828924, AA001202, AI961323, BE277870, AI093113, AI377976, AI951984, AI635625, AI624029, AI418242, AW088095, AI346936, W92652, AA130170, AA024605, W60401, N53543, AI207798, AA969140, AV706224, AA206833, AA862855, AA883077, AW173095, AW467519, BF830518, AI890288, AW952261, AA676671, R76291, AA641764, W60310, AI536758, AA742467, W92685, BF830522, C01747, BF029590, AW273508, W72474, AL047508, AI863984, W46673, AA928559, H97873, W46482, AA969604, T17266, W92828, W94587, BF963436, AA024606, AA973624, R61420, BF107415, AI932612, W76228, N72501, BE147741, AA160170, AI247642, AI499771, AW582120, N92375, AI803849, C04881, AW192182, N67695, R76925, AV728500, BF906742, AA641806, AW601191, BG104607, H00789, T31087, R61378, BE706416, AL047509, R78711, R76567, AA564390, AA992073, C15162, AI187944, AW779277, H39236, AA812071, W61163, H85007, AA733042, W61229, AI016971, H81599, H97053, R78466, H86612, H85630, AV713546, H90060, H86032, R78534, AW952259, AW889353, AA021401, AI540906, W24617, R62435, AA714924, R84855, H00689, H81598, AA918680, BE903841, T08911, BF834059, AA501896, BG106391, R40305, H86526, H85633, AA021275, R21120, H85004, AA774992, AI834279, AW970014, BE140906, N56017, AA573996,

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HCEWE20	44	543370	1 - 871	15 - 885	T51653, AW168798, BG059728, AW151307, AA189081, AL133942, AI924175, AI610776, AI034217, AI479035, BE165748, AI811494, AW090210, AA346162, AW167452, AI687804, AI749571, AA470572, AW089655, AI197934, AI827133, AU144339, N64574, AA470493, AI697247, AI937684, N76274, AI984510, AL047920, AA223830, AA493998, BE176566, AV730063, T62931, BE148908, AA876415, AI801377, AW589501, AA085707, AW177317, AI439860, AI813517, AA581340, AI858607, AA099491, AA613244, AI887321, AA643785, AA633390, AU143906, AV719347, AI362951, W58428, AU146966, AA847621, AI564253, AI921101, AL041417, AA643823, AI567544, AI733077, AW177120, AI561208, AI264673, BE158597, AU145674, AA130536, AA694579, N74502, N54295, AW440317, AF063514, AU119100, AA873103, AW177237, AA160519, AA197059, AW177231, AW177264, AA598786, W49501, AA911409, N26540, BE264670, AL036881, AU146974, AA493751, AW994225, CI7730, AA724159, AU145383, AA157033, AA041332, AA166854, H96719, AA055654, H65500, AA219480, AU148220, AI935333, AL523955, AI132962, AW084901, N48690, AI862874, D29455, AA598990, BE044603, AF074627, AV730577, BG235936, AA878800, R94112, AW275729, AI376984, AI951835, AA101456, AA503213, AW440351, AI735074, AW177266, BE904846, AA846188, AW177226, BE152426, AA493735, AA593081, AW615437, AI538654, AA404968, AW813744, AA669580, F03370, AA350922, AA356989, AI421079, AV728282, AW771706, N76124, AI189033, AA584498, AI961771, AA953572, AV719696, AA467957, H04879, BE159220, T69889, AV720543, H97020, AA467904, AW074001, AF282520.1, AC073310.7, AK026100.1, AL030995.1, AL445236.22, AC023160.31, AK027219.1, AC003977.1, AC008945.6, AJ271735.1, AC012172.6, AL161415.2, AL139125.18, AC002217.1, AC023892.35, AL512629.7, AC069228.26, AC011998.8, AP000075.1, AC008651.7, AL133238.3, AL359816.16, AL121694.4, AP000639.4, AC004029.1, AL121757.7, AC002349.1, AC027304.3, AC004397.1, AF003627.2, AC018637.3, AL355615.12, AB038653.1, AC011755.7, AC022468.5, AL133325.20, AL356113.8, AL121986.12, AC004636.1, AL356213.10, AL390023.8, AC008496.5, AC009812.17, AL136374.4, AC007388.3, AC005280.3, AL133404.8, AC012309.7, X14975.1, AL133240.3, AL158069.16, AC011310.3, AL356782.14, AL158055.12, AC010285.4, Z84482.1, AL359950.4, AL034428.4, AC010145.9, AL441887.9, AC003085.1, Z83836.2, AC025420.26, D86996.1, AC007392.3, AC007207.22, AC020717.3, AC022316.18, AP002532.1, AC012323.7, AC026413.5, AL590792.1, AL031387.4, AC022083.6, AL512885.4, AK021525.1, AC005614.1, AC008162.3, AL136170.12, AF248484.1, AL033524.11, AC079175.24, AC007051.3, AF127577.2, AC016396.5, AL132715.3, AL359398.2, AP000626.5, AC073095.3, AL353580.7, AL354758.14, AJ251973.1, AL034545.1, AC004551.1, AC068812.13, AP001669.1, AL590404.5, AC010276.6, Z73497.1, AC013355.7, AL031775.1, AL049570.11, AL590387.7, AC008518.3, AC003670.1, AL160236.4, Z95114.19, AC025212.5, AC017060.7, AL031224.1, AF127936.2,

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HCFOM18	45	553582	1 - 625	15 - 639	
HCGMD59	46	636078	1 - 776	15 - 790	AI346379, AW009453, AA477432, AA152289, BE219294, T27069, A1745607, AW852105, AI807602, AA234651, AA024744, BE219304, AA065244, N91858, AI242569, AI091032, BF977615, AI251849, H88431, BE301616, N50522, BE762367, AW607675, F03857, H41152, BE696404, R45373, BE070278, H88369, AL039156, AU133046, AL038837, AL039074, AL039564, AL039109, AL039108, AL037051, AL038531, AL039659, AL039625, AL039648, AL039629, AL039678, AL039150, AL039128, AL037726, T79771, AL040992, AL036725, AL045337, AL042909, AL039423, H53427, AL039410, AL045353, AL037526, AL036973, AL044407, AL039538, AL039386, AL044530, AL036196, AL039924, AL039566, AL039509, AL038025, AL039085, AL037639, AL038821, AL036767, AL043423, AL045341, AL037615, AV743601, H53426, AL043422, AV746102, T24119, T24112, AW975143, AV758878, AL036238, AL043441, AL036117, AL043445, AW013814, AV718844, Z99396, AV738934, AL045794, N91869, AV737584, AW973101, BF294063, BF508972, AV743654, AL036924, AW975229, AW979144, AI535983, AV717989, AV717980, AW451070, AV701782, AV718018, AV717988, AV731085, AW973200, AV701012, AV718016, AV717959, AV717984, AW064110, AV718023, AI002696, H00069, AW607606, AV735727, AV717963, AV717962, AV720464, AL036733, AV745724, AV701118, AV717966, AV745723, AV718002, AV719000, AV700229, AV699447,

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HCNDR47	47	1016919	1 - 1329	15 - 1343	<p>AI621217, BF222897, AA632651, AI950250, AW139452, AW207039, AA505117, U69203, AI949187, AW953975, AI160725, BE348367, AI631345, AA707909, AA535510, BG059719, AI680791, AI700776, HI17406, AA524577, AA062981, AA365529, HI16756, AI699070, AW970783, BE858688, AI696027, BF766585, AV709230, BE220337, AW194354, AA365530, AA678861, BE707377, AL122003.17, AB007895. 1.</p>
HCNSB61	48	526413	1 - 698	15 - 712	<p>AW964468, AW975618, AV741221, AW966389, AV738928, AW949645, AV727978, AW966053, AV724520, AV701357, AV738340, AV731070, AW978633, AW964532, C14331, AW966330, AW960553, AV742090, AV723247, AV744012, AV718489, C14429, AW352117, AW752082, AV702035, AW753053, AW177440, D80045, AW949642, AV744690, AV718800, AW360811, AV741220, AW178906, AV718692, AW375405, D59927, AV742048, AV718707, AW973541, AV721784, AW753067, AV701125, AW178893, AV701216, AV701166, AV701149, AV742001, D80268, AV649986, AV720791, T03269, AW377671, C14389, AV649974, AV720211, AW179328, D80134, AA514186, AV701224, AV701154, AW966029, AW752110, AW966075, AW966065, AW960465, AW973334, AW966531, AW978634, AW966534, AW179332, AV742667, AV742022, AW966560, AA305409, D58283, AW966022, AV701335, AV742430, AV744662, AV701043, AW959799, AV701332, AV701017, AV701248, AV701431, AW966059, AV723097, AW966013, D59859, AW964766, D80022, AV726390, AW966041, D80166, AW973474, AW966378, D80195, AW975621, AW978648, D80193, AW975613, D59467, D51423, D59619, AV701443, AW978661, D80210, D51799, AW965163, D80391, D80164, D59275, AV720533, D80240, D80253, AW966030,</p>

					<p>AV719822, AW966054, AV720203, AW366296, AW964756, AW966050, AV719188, AW973307, D80043, D59787, D80227, AW966062, AV719324, AV718440, AV718938, AV719783, AV720028, D59502, AW959597, AV718633, AW959628, AW960473, AW965177, AW975605, AW959570, AV719468, AW965185, AW965197, AW965196, AW973485, AW965184, AW973488, AW965175, AV718931, AV720878, AV718844, AV720464, AV719557, AW360844, AV718770, AV720731, AW973482, AV720150, AV699447, AW378532, AW958992, AW958993, AV722801, AV723927, AW959136, AW956397, AW959062, AW964477, AW956434, AV699550, AW964488, AW949641, AW962082, AW949656, AW360817, AW949654, AV699927, AW177501, AW959202, AW177511, D80132, AV720151, D81030, AV699746, AW375406, AV726921, AW378534, AW973490, D80212, AW377672, D80196, D80188, AW179023, AV741187, AW178905, AV741198, AV741191, D80219, AW973468, BF349328, AV705680, AV649966, AW973423, AV718530, AW962395, AV650003, AV701123, AW973470, AV699866, AW973473, AA305578, AW973445, C15076, D80038, D59610, D80366, D57483, AW179329, AV720616, AV701130, AV701419, D51022, AV701422, AV758213, AW966043, D81026, D50979, D50995, D59889, AW753041, AW178762, AW962245, AW973447, C14014, AW966023, D80024, AW959469, AW964737, AW960454, AW966032, AF271371.1, D34614.1, X67155.2, AF058696.1, D88547.1, AB028859.1, D50010.1, AB002449.1, U79457.1, AB038216.1.</p>
HCQCT05	49	911924	1 - 665	15 - 679	<p>BF691828, BE463583, C06338, AA826324, AA622862, AI890787, AA775044, BE566444, AA621523, BF207929, BF208992, BE928360, BE568426, AW873470, BF036636, AI632964.</p>
HCUGM86	50	847040	1 - 613	15 - 627	AA722669, AC005035. 1.
HCUIM65	51	550208	1 - 861	15 - 875	<p>BE781101, BE540200, AI972511, BE300952, AA464837, BG150212, AI681901, AW172458, AA099207, AW205564, AW408650, AW205714, AA450308, AA636047, AI656442, BF437116, BE466112, AW575656, AW962721, AW206882, AA099221, AI620473, AA369585, AW469939, AW136836, BE547752, AI638262, BF059133, AA236642, BE551958, AW086133, AI917742, AI623315, AC005391.1, AL445584. 16.</p>
HCWKC15	53	553621	1 - 696	15 - 710	<p>AW504485, AI380617, AW805539, AV758903, AL079734, AA916430, AW819125, AV762982, AI625604, AI792575, AW084445, AW975210, BE138594, AW069227, AW023111, AV764259, AI792521, BE501593, AW021583, AI890324, BF725844, AW438542, BE138509, AV763026, AV763058, AA904275, AI521525, AA665330, BE077105, AA501461, AW969743, AW327591, AA535216, R94326, BF589824, AA574442, AW338179, AW271904, AI279417, AA651639, AI859946, AA524616, AW020150, AA833896, AV761862, AL042373, BE968744, AW004884, BF528591, AV760019, AA610509, AU131037, BF804385, AA833875, BF725761, AI053688, AI923052, AV761714, AI821714, AI792133, AI791913, AA013168, T74524, AI355246, AW474168, AI284543, BF724838, AI912401, AW068596, AV762633, AI564209, AW975626, AI620992, AI821785, AA483606, AV756220, AV754716, AA533176, BG236628, AI491765, H05940, BE139139, AA504906, AI250552, AA019973, BE049032, AA223174, AI798449, AA570740, BF965775, AL022238.1, AC006329.5, AL359402.3, Z98304.1, AC006948.4, Z84487.2, AC006312.8, AC026749.5, AC010627.5,</p>

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				15 - 1428	AW967979, AA937109, AA465498, AA465250, AW967765, AA262829, AA743297, H93605,
				1 - 1414	
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HCWUM5					

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HDABR72	55	1301517	1 - 1677	15 - 1691		BE294597, AA749068, AI284640, AL046409, BF677892, AW193265, AI431303, AL138265, AI334443, AV760777, AI613280, AV763354, AW419262, BF668217, AV760937, AI963720, AV740801, AI281881, AF330238, AI345654, AW502975, AV710066, AI270117, BG249643, AI305766, BF311000, BG109996, AV762098, AV734666, AW965008, AW576391, BF337291, AV762050, AV761362, AA610491, AW410400, AW833862, AL045053, AI345518, AL138455, AW327868, AV728425, AI350211, AW270270, BE047069, BF697673, AV735370, AW500125, AV764307, AV761489, AV762111, AV764578, AV762395, AA631507, AV725423, AV763255, AV763971, BF679304, BG222267, AA526787, AL044940, F36273, AA469451, AI610159, AL041690, AV759274, AV761786, AL119691, AI305547, AA490183, AI754658, AV762139, AL037683, AI821271, BF241967, BG236735, AV757607, AI568678, BE350475, AV764241, AA491814, AW872676, AI708009, AA720702, AW472872, BG059568, AI053672, AW963497, AI133164, BF827410, AL042420, AW439558, AI289067, AW969629, AW974109, BG171096, AW438643, AI355206, BF681576, AL046205, AW276827, AV760774, AV762064, AV756693, AV652936, AL120687, BF130107, AI149478, AW975425, AV763633, BE049139, AA468131, AI471481, AV760042, AI688846, AV762959, BF854876, AV759505, AW269488, AV764398, AI537506, AV762397, AV763670, AV658688, BF940837, AV763195, BE154617, AW088202, AW407578, AI679782, AW630298, AV762535, BE872393, AI619997, AI341664, AI345681, AI345675, AI801482, AV733830, AF074677, AW406162, AW103758, AV763540, AV762154, AW193432, BF475381, BF964720, AA623002, AI375710, AV682003, AV759382, AV757425, AW083402, AI633025, AW972769, AW029038, AW511743, BE042649, AI053790, AV762009, AI919265, BG104686, AW021207, BF724372, AI061334, AA984708, AV760057, AU151000, AU145314, BF939954, AI499938, AW406755, AI085719, AV763122, BF851403, BE049095, AW148792, AV759580, BE206443, AI799642, AW023672, AV761843, AW162049, AI962050, AI929531, BF680805, AA483223, AW088846, AI281697, AW969698, AW969694, AI732865, BF679274, BF984160, BG056088, AV761403, AW872575, AV762826, AL119649, AV761106, AI446601, AI249997, AI434695, BF793766, AV761188, AW979031, BC003642.1, AC018795.9, AC005280.3, D83989.1, AC022148.5, AF077058.1, AC009161.12, AC002470.17, AC083868.2, AF015151.1, AL022724.2, Z93023.1, AP001666.1, AC007308.13, U18391.1, U18392.1, X55925.1, AC084882.2, AL590964.8, AF015149.1, AF015156.1, U57005.1, U57006.1, U18394.1, AC009086.5, X53550.1, AL031123.14, AC073655.26, AC012077.4, U57008.1, AC004862.1, AC009475.4, AC008039.1, X55926.1, U57009.1, AC006211.1, U18395.1, AF015157.1, AP000901.5, U18393.1, U57004.1, AL137839.6, AF015147.1, AL031121.5, AC009952.4, AL049759.10, AP001725.1, AC007367.3, U57007.1, X54180.1, AC008760.6, AP000557.2, X54181.1, X54178.1, AC021752.5, X75335.1,

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HDPBA28	56	1062783	1 - 3433	15 - 3447	T27258, AU140225, A1634860, A1767588, BE536545, AV689583, A1991689, A1635347, BE386012, BE767008, AW976840, A1640606, BE178142, BE177971, AW502888, AA977785, A1979247, AW503911, AA971157, AL135446, T27536, AA491080, W74279, R07065, A1687230, T27535, AW816221, AA436906, BE151455, BF510035, BF803181, BE151443, AA152394, AW505067, BG003144, AA761110, AA377229, AV648450, BE671931, A1873792, AA397568, AA399529, AA679080, A1382296, AV648107, AV648212, AV648537, A1913234, A1741350, R50230, A1920850, A1018184, AA702114, A1244588, R81654, A1126673, AA152500, BG057181, AA148355, BE817269, AF222340.1, AF183569.1, AF106037.1, AB011097.1, AC008906.5, AC009073.8.
HDPCJ91	58	740748	1 - 6093	15 - 6107	AU119039, AW959367, BF792861, BF672087, BE439439, BE717153, BE770928, BE718895,



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HDPCL63	59	1019008	1 - 3023	15 - 3037	<p>AL040501, AL040502, BF312113, BF311401, BF312099, BF969955, BG118304, BE889750, BF528529, BE892499, BE378197, BE796737, BE312325, AL043139, BG033292, BE314857, BE312562, AW961051, BE875599, BE395864, BF528758, BF312036, BF982580, BF511000, BF206591, BF689722, BE278785, BE301032, BE538635, BF062495, A1074169, BF063302, BF528817, BE550763, A1439151, BF568696, A1432267, BE044341, A534289, A1968616, BE644848, A1374815, AA025730, A1718363, AA984833, BE893882, AW084880, AW952114, BG012441, A722825, AA514696, A1809529, BF835155, BF892650, A932271, BF739765, BF894752, BG059761, A134803, A1828209, AA460484, A1042088, A134802, A1640382, R51678, A1925709, A1669079, AW469179, A1199232, BF900427, R53751, BF349740, BE279833, BE273231, A1640403, A1074545, BF753080, AW579547, BE731727, A1659329, AW002463, A2333548, A1003456, BG222370, AW137214, AA230095, T55730, H43116, AW962595, BF001788, A1670726, AA626289, BF910860, AV748998, AW276888, AA323567, AA233662, Z45129, H45702, BE245940, BE383639, R40971, R53750, AA037073, T03319, BF813413, BE074131, BF691850, BE244555, BE146067, BF924555, BF244566, A1141636, AA339051, H45753, BF691075, BF690883, H42344, AA291701, A1884572, AA356368, AW080418, AW071165, AW296941, AA631213, AA317597, R39383, AA324321, BE244793, BF221497, A1278324, BF977743, AA025729, BF055230, R10660, AA429477, A1468432, AA291748, A1537969, H52665, U46451, A1979165, BF570791, AA378387, A1918383, BF923133, AA455817, AW103386, BF868375, BF868370, AA922522, BF977581, R38308, Z39044, R51590, BF737690, BF976877, R12982, F04029, A1868824, T55772, AW263568, AA233779, R14452, T31372, AA292264, AA287135, A1560594, BF691578, AV743961, AA284706, BF894453, Z42923, AW152063, A1916442, BE694236, AA338803, BE049333,</p>

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HDP025	60	460682	1 - 753	15 - 767	
HDP0701	61	771583	1 - 2673	15 - 2687	AL524311, BG251269, BF310537, AU133126, BF683381, BF038290, AW732293, BF316433, AW170099, AI056333, BF349288, AA972732, AI675184, AW177595, BE141799, AW664330, BG056730, AW751928, BE141798, AU157403, AI803604, AW516199, AI421509, AI089433, AA622275, AU154510, AA699595, AW733094, BF838983, AI148225, AA921836, AA701632, AI361562, H75815, AV701643, AA931757, AA825979, BE837455, AI247022, AA035572, AI015040, AI032666, AW167576, T89750, BF349289, H06815, AI168573, AI702086, W42567, Z43621, AA505697, R92850, AI204070, AA724075, H06816, W72651, R93066, W76613, W42546, W86249, AW751931, AI272047, T16739, AI868745, AA860360, AI207229, AI249348, AI073394, AA035062, AA758712, AI204396, T11609, AA649046, AI168656, AA729782, AL110209.1, AL389957.1, AK001705.1, AB017494. 1.
HDPH151	62	460679	1 - 714	15 - 728	AC005946.1, AC018755. 3.
HDPJM30	63	879325	1 - 1621	15 - 1635	AI420713, BF951818, R85260, H28149, BF899899, BF594396, AW292642, H44846, BF685411, AI739196, AI867313, BF063759, AI380559, BE504664, AW166357, BE735346, BF064117, AB001535.1, AP001754.1, AP001065.1, AP001064. 1.
HDPND46	64	637586	1 - 1713	15 - 1727	BG058578, D20888, AL034424. 9.
HDPOJ08	65	731863	1 - 1641	15 - 1655	BF968799, BF791555, AL513581, BE879926, AI949941, BE827843, BF968555, AI765763, BE875907, AW959968, AW382167, BF692458, BE876162, BF106234, AV713629, AV699640, AW382174, AU136532, BF692025, AA449500, AW902068, AW583040, BF212019, AW382170, AI768711, AI918137, AW235520, AI199832, AI074542, AA243341, AA071031, AL513582, AI308913, BE150978, AW609396, AA604828, AA831297, AI304674, BE151243, AW391610, AA704776, BE150919,

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HDPN86	66	1037893	1 - 6283	15 - 6297		<p>BE250002, BE394338, AW935469, AW749660, BG250570, BF982358, AI821271, BE541597, AI313180, BE293706, BE872198, W22478, AW976010, AI002815, AW963152, AU117456, AV762145, AV760760, BF792326, AW965008, AV764490, AW837083, AV700498, BG032943, AW600804, AV733710, AV759172, AA680243, AU123691, BE908796, AL037632, BE796439, AI076616, AW406162, AI732120, BF339640, AV700988, AA484962, AV699709, AW965642, AF074667, BE902459, AV760599, BG164166, BE273856, AI313166, AU118745, BE387734, AW961994, AA381195, AI364780, AU159301, AV761286, AA722372, AU158602, BE154495, AL044000, BG250302, AL041706, AL040921, AV700545, AU145083, AI817516, AV729960, AV760258, AW820787, BE071876, BF965477, BE071877, AW974126, AV759362, AI565581, AI284640, AI963600, AI608771, AL048626, AW440545, BF677892, AI204304, BE902975, AW317075, AA836811, AW088224, BF337291, AA634072, AI350211, AV704375, AV760777, AW193265, BF668217, AI133164, AV762395, BF736198, AW953071, AU157011, AW833862, BF241967, AL046409, AW995093, AV711987, AA491814, N94311, AI431303, AI963720, AW276817, BF828714, AI613280, AV762098, AA601355, BG249643, BF697673, AF330238, AV760937, AV728425, AW080939, AA599480, AV740801, BE156019, AI924251, AA469451, F36273, AV658688, BF055844, AI289067, AL119691, AV763354, AI061334, AV763971, BG058664, BF680074, AV725423, AL045053, AW970915, AW975425, AI471481, AI305766, AL138265, BE350475, AI679294, AA205915, AI754955, AL137737.1, BC001041.1, AK000310.1, AC010366.5, AC005280.3, AL137852.15, AC022148.5, AC004263.1, AP001666.1, AP001630.1, AE006463.1, AL354932.26, AC005484.2, AL590762.1, AF088219.1, AC007782.20, AC004134.1, AC005288.1, AC011811.42, AC005911.6, AL161656.20, AC072052.6, AC009470.4, U47924.1, AC004859.2, AL035587.5, AL162505.20, AC073138.3, AC025166.7, AL359552.16, AC007954.7, AC034242.5, AL139317.5, AC011455.6,</p>

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HDPSB18	67	1043263			

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HDP5H53	68	1309174	1 - 1649	15 - 1663	

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HDPSP54	70	744440	1 - 3077	15 - 3091	BG256849, BG261011, BG178729, BG110345, A1923220, BE466885, BF667257, AW271504, AW243442, BE466659, BG171469, AV661528, AW271637, AW516811, N36059, AI804888, BE882420, AI650826, BF815232, AW964507, AI921747, BE936373, BF984751, BG259707, AI392784, AW076096, AI807747, AW103424, AA604757, AA633209, AW778887, AW418987, AW242326, BE622192, BF666519, BF978796, AW014203, AI925261, BF853590, AW131363, AW514756, N33223, AI819108, AI126250, AV649748, AI953896, AV714556, AI524472, BF697124, BE218100, AW629098, N21567, AI694687, AI700209, AA731730, AA577191, BE219931, N33824, BE567212, AW778908, AW087660, AI990562, BF792681, R52426, AI559108, AA743389, N35579, N25189, N30972, BF667662, AI339587, N24947, AI376459, AA742979, N27426, R23308, AI125720, AA954281, AI801129, AW087669, AI701246, AI245517, T26975, BF572334, BE177998, BE564497, AI636147, AI640713, N41938, H97662, AI243263, BE967025, AI572028, BE543895, H29641, BE762905, BF246305, Z46022, H29640, BG223352, AI270534, AI983198, H99399, BF965116, BF692452, Z42169, AI521060, BF102948, R82562, AV646807, N34709, AV646406, R23233, AA373475, BE005657, AA319637, T34245, BG104469, W20047, AW962829, BF572695, AI369988, AI741908, BE830524, H29549, D78710, Z41637, H29548, AA833897, AI367191, AA659275, AW899997, F01708, BF697465, AI246035,



HDPUH26	71	866433	1 - 2902	15 - 2916	AI219239, BF154447, AI221561, AI273738, AI281168, BE005723, BE170424, AI685342, BE882847, AB007962. 1.
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HDPWU68	72	812737	1 - 1734	15 - 1748	AW295848, AI132995, T48851, AI247571, AW469884, AV734061, T48852, BE378325, AW571432, AA344713, AW131386, AU138048, AW190967, BF896891, AA400508, AA400618, AA835515, AF170485.1, AJ007395.1, AJ130710.1, AF193441.1, AJ130711.1, AF227924.1, AB026265.1, AF247180.1, AF178981.1, AF223403.1, AF195092.1, AC020914.7, AF277806.1, AC011473.4, AF135027.1, AF310234.1, AF287892.1, AC008750.7, AJ130712.1, AJ130713.1, D86359.1, D86358.1, U71382. 1.
HDPWU34	73	630354	1 - 1263	15 - 1277	BG054851, BF439942, AI141684, BG008949, BE677186, AA242853, AI281834, BF433831, N50984, AA826047, AW014432, AA977801, AW770255, AA984041, T64272, AA994205, AA252172, T64144, AI361098, BE146421, AW084330, AI280735, AA931748, AW071613, R09320, AA448980, AI990634, R09211, AW388104, AI147841, AI198101, AW517751, AW238793, BF969846, AI627898, AU156992, AW074546, AW072130, AI276023, AI457707, AI394689, AI953242, AI539262, BE907440, BF984530, AI886594, AA761557, AW082532, AI613471, AA947158, AI380329, AW079334, AI636788, D44958, AI568132, AI274769, AA150147, AI624304, BF828567, AI933785, AW248417, AL036548, AI934147, AI343038, AW302662, AI336506, AI254251, AW303238, BF054886, AW268290, AI318301, AI866691, AI627621, AW263569, BG028962, BF792115, AW073898, BE877316, AI805688, BE874060, AI554218, AI445620, AW151652, BF055737, AI335411, AL043084, AI537190, AI445812, AI890057, AI889133, AV709604, AV703599, AW050725, AI355779, AI537516, AW149876, AI679261, AL040011, AI690927, AV743631, AI539771, AI249877, AW152214, AI340570, AW411412, BG178911, AI926593, AW301381, AI888621, AI357599, BF911528, BF909758, AI677983, AA088789, AW129993, AI623797, AW055252, AI628188, AI539632, AI349017, AL037521, BE138941, AI696626, AI432237, AI349762,

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HDPXY01	74	879048	1 - 752	15 - 766	AW860154, AW860153, AW821875, BE869510, BF094022, BF337555, BF527692, AW845544, AW176604, BF734241, BF928740, BF360615, BE169703, AJ230819, BF734231, AL133649.1, AJ271791.1, AJ271790.1.
HDTBV77	75	785879	1 - 2167	15 - 2181	BF689672, BE387282, BE898209, BE386984, AA393894, BE893192, W22615, AA134750, BG006306, AI769121, BG006608, AA808986, AA367857, AA344170, BG013403, BF368795, AA367892, AW605363, BG006302, BF932070, AW948496, AK027375.1, BC004282.1, AK027831.1, AK027849.1.
HDTDQ23	76	1306984	1 - 2193	15 - 2207	AI872206, BF966561, AW513884, AI912340, BE856991, AI758821, AW337178, BE327923, AW004890, AI572080, BG109128, AW058001, BF342854, AW868887, BF967940, AW474823, BF337371, BF591084, AA775261, BG164538, AA831357, BE087219, AW074361, AI361820, BF696525, AI982775, BF793075, AI690445, AA581345, AU156793, AI917776, D20022, AA825538, BF382552, AI360561, AW439592, AI798286, AI140796, AI277190, AA100279, AA485257, AA835492, AI522238, AW517943, BG035022, AI015234, AA706811, AI469550, BF197859, AI689240, AW265061, AI744762, AW450726, AI884872, BE714642, BE138867, T34498, BF213985, AW769512, BE073192, AA122332, BE138831, BF090537, AI811224, BG167993, BE932894, BF980823, AI355770, AA092467, AI471817, BE904497, BE719958, AI702026, BE171537, BG166879, AI597962, BG180321, BE171499, BF914841, BF967213, BE932875, AI681670, AA089786, BE327680, BE219939, BF032916, AU136610, AI624976, AK001917.1, AF035606.1, U58773.1.
HE2DE47	77	619852	1 - 3519	15 - 3533	AL517387, AL526769, AL526907, AL523193, AL523194, AL515001, AL515002, BG030741, BF980577, BE903049, BE729941, BG163644, BE966268, BE067770, BE613706, BE780216, AL138389, BF196312, BG177870, AI041824, BE902470, BE384275, AI123426, BE384622, BE298710, BE067771, BE298416, BE885382, AI432657, BF966758, BF979153, AI708574, AI814491, BF036235, BF437789, AI720253, AI201638, AW182430, BF692903, BE867186, AA911185, BE748929, AW189237, AI432659, BE223052, AI687145, BF382011, BE564813, BG036747, AI024779, BE268867, AW029376, BF028837, AI024507, AW880654, N47923, AA706430, AA563625, AW662575, BG111471, BE748409, AA232692,

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HE2NV57	78	740750	1 - 853	15 - 867	C05927, R72949, AA327984, AC084730.2, AC016673.5, AC004929.2, AC016716.6, AC008066.4, AC003969.1, AC024082.6, AC002302.1, AC013246.13, AC011490.7, AL158064.16, AC084729.2, AC078851.4, Z98743.1, AC020610.6, AF195953.1, AC016910.5, AL359394.9, AC005227.2, AC003692.1, AC016776.6, AC002300.1, AL451107.6, AL157838.24, AL031737.2, AL050335.32, AC007690.11, AC004541.1, AL022401.1, AC018796.4, AL358913.4, AL008583.1, AC005868.1, AL133383.10, AC006070.1, AC006211.1, AL359680.4, AL158035.14, AC087072.2, AC009424.2, AL391686.10, AP001684.1, AC006013.3, AL356461.15, AC016598.5, AP002980.2, AL158817.11, AL035685.21, AC034251.5, AC006134.1, AC020906.6, AL391241.21, AC015983.7, AP003470.2, AP001889.4, AL357519.19, AC087430.2, AC005081.3, AC005886.2, AC018509.5, AF277315.3, AC010913.9, AB020875.1, AJ011930.1, AL163300.2, AP000952.2, AL133387.8, AP000953.2, AL162503.12, AC025765.5, AP002342.3, AL445232.5, AC023114.5, AC004891.1, AL355792.8, AL163280.2, AL109662.3, AC010206.8, AL049843.18, AC017076.14, AC009362.8, AC005015.2, AL096791.12, AC002487.1, AC010726.4, AL353752.6, AP002846.2, AC005344.1, AC022363.24, AC009498.3, AP001699.1, AL138976.5,

HE2PH36	79	570903	1 - 1544		AC008064.2, AL357507.9, AP001670.1, AL137061. 12. AA329666, AA664883, AL133353. 6.
HE8DS15	80	847060	1 - 2185	15 - 1558 15 - 2199	AV725650, BE161426, AW130367, BF343057, AA127680, BF575221, A1096437, BF941499, W58383, A1161240, N95226, AW966449, A1356752, A1093508, A1057144, AA044288, AW130361, A1423547, A1221152, A1094774, H47283, A1352542, A1891136, A1002491, T53270, AA044116, R48378, R24320, AV658066, A1829703, A1819388, BE140169, Z44849, R16574, T39273, AA095159, Z25099, AW273857, R16633, AA384077, A1245095, AW026140, T93764, BE927909, N73937, AW118768, AA121543, AA995178, A1453845, AA703455, A1452494, AW044037, H40993, R48277, AW629019, T64039, AA904647, AW073189, W21055, AW263913, A1096938, Z28777, W03697, AW797518, A1039546, A1434419, AW050649, BG003285, A1240412, AA886341, H23905, A1695284, A1767991, H47284, A1309041, BE927916, AA724059, A1352281, A1584012, AA618131, AA357401, A1796309, BE936061, AB018301.1, AL096772. 5.
HE9CO69	81	596829	1 - 1063	15 - 1077	AL517134, AL537534, BG120134, A1361222, A1361218, BG168891, A1818146, AW955091, AL044002, AV719782, AW510853, BF699219, A1937067, BF216510, BE927666, AW292803, BF335422, BE549610, BE927669, BF680792, BE881703, AW444975, BF085414, A1809804, BF674861, AA643669, AL044003, BF085327, AW571754, A1870371, A1333293, AW804029, BF367442, A1027392, BE825418, AW804094, BE814966, BE004566, AW804040, BE814989, AW804038, BE178594, BE814978, BE694316, AW804031, BE815035, AW804096, AW935907, N51364, W52337, A1140675, A1159864, BE178632, A1949007, AA449305, A1279860, BE927615, A1912517, A1056498, N66531, BF085618, A1344560, A1571128, AW887696, AA448734, A1937064, AA908864, BG150261, AA620750, BF085472, BE004562, BF197164, BF689123, AW102597, AL524051, BG150351, AA515676, AA845306, BE178588, BF433188, AA084404, AA448757, A1825137, BE178649, H12900, A1356775, BG167519, AA523074, AV756035, W49814, AW189236, AA448798, BF516003, H99378, A1313393, D82523, AW804120, AL517135, N89941, A1830723, AW887703, AW887694, N57002, BF085413, A1348377, A1423892, BE004603, AW887709, AA961085, BF085333, A1380140, A1423619, AA772080, D82499, A1244153, D60492, N64261, A1225085, BE089349, AA907447, BE089348, AW001668, BE825346, BF352382, BE089337, BE815028, A1289220, AW241615, AW052165, BG168918, R48783, BE814984, A1767167, AW472798, BE815055, A1423765, H00809, D57482, BF327548, R17701, R16274, R15770, AW024854, R28195, D82446, N88488, F09950, A1655533, H08546, Z30216, T30774, H12901, BF327564, BF037045, D82493, C02460, R28196, D57590, AW089369, BF111213, BF668534, T95086, BF437738, BF677346, D82563, BF327550, R38734, A1268405, AW440038, BE004951, T34027, W33131, H16803, BE004551, R56288, BF691993, BE927656, BE004811, D82528, AL532423, AV725074, D54250, BE927693, T95183, D82529, AL537535, T11295, W31584, W32076, R48890, BF688163, W33132, BE815060, BE004800, AW804018, BE004907, BE004864, AW804090, C02521, AW887690, A1674883, BE815026, BE004960, BE856297, BF327561, AW954918, BE868208, BE178643, BE004763, AA449562, AL515196, BE004560, BE089347, BC003074.1, BC005959.1, AC006033. 2.

HEEAG23	84	684254	I - 1655	I5 - 1669	<p>BF667852, AW798053, BG141339, AI279852, BG141348, H57654, AI472339, H85172, BF879975, BF879989, BF879974, AW954063, AW994019, BF590284, AA383569, H96534, BF800241, AA903404, AW873530, AA719530, AI084916, AW135894, AA993772, BF358415, AA890589, BG249829, W61170, AA807443, AW498471, AA814409, BG149771, AI828884, BE839816, BF954921, R76166, BE545018, AA470533, BF922076, AI829062, BE766575, BF808213, AA737653, H96878, R62923, AA714658, BF808212, AA705115, AI964064, AA569749, AI343340, AC004938.2, AL357033.19, AL121808.4, AL135749.3, AL359402.3, AC009314.4, AL031777.4, AL035079.14, AC078818.19, AL358612.8, AC018644.6, AL391839.9, AC013716.6, AC004882.2, AL078591.18, AL078645.31, AL031680.20, AL162505.20, AP001715.1, AC025264.16, AL109938.8, AC006312.8, AF243527.1, AL133367.4, AC010319.7, AC083875.1, AL050349.27, AL162615.13, AL356575.8, AP000223.1, AL121578.1, AC084732.1, AC005033.1, AC005082.3, AL136162.17, AC027319.5, AC062020.5, AL157915.3, U63313.1, AC006511.5, AC011443.6, AP001687.1, AC004477.1, AC011508.4, AC083866.2, AC006315.2, Z84572.1, AL136131.15, AC011005.7, AP001429.2, AL035462.21, Z83823.1, AC002350.1, AL138820.11, AC020896.5, AC010206.8, AC011495.6, D83253.1, AC004151.1, AC008813.6, AC005291.1, AL354696.11, AC005225.2, AC004652.1, AC083810.16, AL390071.9, AL021940.1, AP002907.2, AP000962.2, AL031721.1, AL031666.6, AL353807.18, AC004167.1, AL009183.10, AL356095.11, U78027.1, AC018763.5, AL021393.1, AL391114.12, AL121928.13, AC068799.14, AC004223.1, AC004846.2, AC002400.1, AC004867.5, AF141309.1, AC006101.3, AL390298.13, AL136297.3, AL035422.12, AL022100.13, AL355593.21, AC010374.5, AC011485.6, AL049643.12, AC008886.5, AC020916.7, AC005694.3, AL139385.12, AC003006.1, AL035659.22, AL022165.1, AC007066.4, AC022816.15, AC068312.4, AL133448.4, AL080243.21, AP000755.4, AC025430.5, AC011510.7, AC064878.9, AL139415.10, AL391137.11, AL356481.16, AC007561.4, AL133387.8, AC011900.6, AL137100.4, AC007014.1, AC067956.3, AL121712.27, AL121809.6, AL159191.4, AC069246.5, AC019171.4, AC004752.1, AL031427.15, Y18000.1, AC004832.3, AC066589.3, AC003065.1, AC073115.5, AC006028.3, AL353746.6, AC005800.1, AC090885.1, AC006515.7, AP001284.5, AC006011.2, AL035587.5, AC006017.2, AL121943.22, AP001698.1, AL445685.17, AC011477.5, AC018648.5, AL352979.4, AC016995.4, AC022401.3, AL133467.4, AL135978.4, AC004913.2, AC005387.1, AP000045.1, AL138707.10, AC023105.7, AC002039.1, AC018755.3, AC023137.5, AL117258.4, AC004076.1, AL513131.1, AC008844.5, AC018636.4, AL353657.26, AL031228.1, AL450344.4, AC006319.3, AD000092.1, AL157789.6, AC006049.1, AC011461.4, AL133284.13, AL121934.17, AL022316.2, AC008392.6, AC010677.4, AC006205.7, Z82244.1, AL139388.4, AL139322.13, AC012476.8, AC022415.5, AC068976.5, AC005393.1, AC006057.5, AC007324.55, AC020904.6, AC026464.6, AP001692.1, AP001724.1, AL139317.5, AC007003.4, AC009779.18, AP000963.2, AP000228.1, AC007919.18, AL499628.1, AC007051.3, AC010422.7, AC011718.2, AC006127.1, AL135927.14, AC007227.3, AC005696.1, AC004754.1, AL359236.4, AC026753.5, AC004534.1, AL356414.11, Z86090.10, AF107885.2,</p>
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HEOMQ63	85	603533	1 - 1322	15 - 1336	AP000547.1, AC010530.7, AC020740.5, AL162426.20, AC005488.2, AL034372.33, AP000689.1, AC037492.5, AL035409.15, AC005037.2, AL049793.4, Z97196.1, AP000140.1, AC009743.1, AP000359.1, AP000088.1, AL357312.8, AL590682.9, AA252707, AA252834.
HEPAB80	86	1307790	1 - 785	15 - 799	BG026315, AW102828, AI659843, BE551400, AI640582, BE208434, BF510823, AW955647, BE669917, AA789132, AA9233523, W44769, AI346827, AI092608, BE267189, AW450220, AI350733, AW090676, AA830093, N98535, N69933, BF694104, AI000893, AI379944, AW968025, AA252680, AI202595, N32022, AL522177, AI026801, BF514413, AA075433, BG014214, AW452208, BE694426, BG171349, AI335272, AI634906, BE796712, AA846518, AA954353, AL522176, AI863776, BE265224, BF359220, BF359223, AW386074, BG112515, AV662306, AA973539, AA329532, F22685, AW136310, N28654, BG014217, AA610002, BG014216, C02160, W37089, N51549, AA361150, BC005984.1, AL109657.8, AL161659.17, AK025977. 1.
HFABG18	87	847073	1 - 1331	15 - 1345	AW274007, AI677890, AW510786, AW468943, AA335322, AI807924, AW172560, AC006116.1, AC011506. 3.
HFABH95	88	566712	1 - 1333	15 - 1347	BF570393, BF569907, BF344166, AA758023, W63573, AA877107, AW664584, AI924890, BE207784, AI422142, AI811174, AI891097, AI379416, AA631138, AI129321, AA233722, AA861574, AI339443, AW009533, AA635649, AA910314, BF510307, AA948287, AA421401, AA621181, H52254, AA908447, BF127938, AA330666, AA458586, AA328941, AI472877, BF337899, AA853185, R69866, AA852144, BF999691, T49327, AA677036, AW024548, R46515, R69911, BF999694, AW593365, H52351, AA976306, BF903330, T49326, AA233143, AI381786, BE827715, AA359077, AI569251, AI685425, AI826541.
HFAEF57	89	534142	1 - 628	15 - 642	BF035708, AI431513, AA832175, AI251429, AV729905, AV754716, AI538491, AI122466, AI446474, AC005006.2, AC008747.5, AC008805.7, AL160155.19, AC005081.3, AC013751.6, AC006241.1, AC004216.1, AL137853.12, AC069285.8, AL590762.1, AC004491.1, AL035659.22, AL158040.13, AL022323.7, AL160411.25, AC005231.2, AC005952.1, AC008649.6, AC002059.3, AL355480.22, AC007850.29, AC024163.2, AP000501.1, Z98304.1, AL122035.6, AC008569.6, AL360227.17, AP000694.1, AC005480.3, AC009470.4, AC008392.6, AC011464.5, AC005911.6, AC008440.8, AC013734.4, AL034417.14, AL139082.18, AC005242.1, AP000511.1, AC008403.6, AC040160.4, AL353653.19, AP001725.1, AL049776.3, AC004148.1, AC007686.5, Z98946.15, AC007374.6, AL137787.11, AC000159.6, AL109984.14, AC002350.1, AC009087.4, AP000351.3, AF240786.1, AC005037.2, AC011490.7, AL022238.1, AC006101.3, AL356481.16, AC005971.5, AC010458.5, AC025588.1, AC005072.2, AL359091.10, AC008521.5, AC016831.1, AL117330.6, AC006312.8, AC007055.3, AC024561.4, Z83826.12, AF196969.1, AC002300.1, AL121891.22, AC005594.1, AC010319.7, AL022322.1, AL513008.14, AC008623.4, Z83838.2, AC005972.1, AC006084.1, AL117694.5, AC008119.6, AP001711.1, AC005102.1, AC004840.3, AL133174.15, AP002453.3, Z83844. 5.
HFCEB37	90	411345	1 - 788	15 - 802	AV655597, AW967329, AW963498, AV706016, AW966767, AL121984. 14.
					AW971191, BE710287, AA493766, D56115, H06701, Z41729, AA285136, AA256963, F04210,

HFFAD59	91	520369	1 - 456	15 - 470	AL118652, AW893768, AW893769, AW160783, AF258348.1, AC007552.4, AL050152.1, AV699250, AV662248, AV699269, AV719565.
HFGAD82	92	513669	1 - 1867	15 - 1881	AL119979, BF346635, AV726399, BF035097, AV727342, AL119977, BF920864, AW888751, N31682, AW148844, AA772781, AA326677, N23200, AW961610, BF976989, BE765872, BE765749, BE765443, BF570590, BE765618, BF438771, BE766953, BE766490, F06586, BG057153, R60278, F07047, AA628815, AV722183, R16237, BF364146, AA204942, AV734361, N71200, AI000462, R54067, Z40722, BF337123, R54066, AW903171, H24278, AV726415, H16893, AW897545, H16783, H22887, R16238, F03521, R42035, F05678, T80483, AA321847, AV731162, AV731097, AV730504, AV730299, AV731130, BE763530, R20855, AA386266, AW890775, R45969, R42611, N94832, R39831, F02857, F03323, T03048, R11992, F07675, AU118413, AW890773, AA640468, N95708, F05679, BE830656, BF948144, M85660, AL119687, T08757, AV722325, AW904904, BF344999, AI003266, N76471, N47227, AW903272, BF977690, T53097, BF918689, F01937, N58994, AI000789, AW898733, BE702498, BE699153, AL118827, BE708346, F07242, AW897547, F01938, N51309, AC003037.1, AC022486.4, AC007379.2, AC007064.27, AC006548.20, AC016752.2, AC008175.2, AC007965.3, AC007322.4, T66696, T66697.
HFIIN69	93	1011487	1 - 1436	15 - 1450	AA448034, AA602540, AA719535, AC018927.6, AC022007.3, AC018809.4, AC007546.5, AC002470.17, AB020872.1, AL035404.20, AL009181.1, AC005102.1, AC007686.5, AC007207.22, AC018808.4, AL109758.2, AL049759.10, AC007308.13, AC002301.1, AC007192.1.
HFIUR10	94	532060	1 - 527	15 - 541	BF195618, AA191239, AW969824, AA009856, AW019964, AA808036, BE677291, AW973259, AW023662, AV742957, AU146063, AI369580, BG109444, AU153717, AV709074, BG032605, AI357823, AW888719, AL110373, AI832009, AV708388, AV725797, BE150580, AA223512, AV734980, AA402529, AA595661, AW410201, AA683069, AA191418, AI144036, AW474168, BF681348, AI590458, AI590499, F08248, AW302048, AV760508, BE794962, AA665181, H07953, AW971071, AA654781, AV763410, AA749035, BF965290, AI609972, BF676985, AV708385, AW504485, AV762633, AW166808, AA282951, AI860535, AI792575, AA634889, AW302950, AL048060, AI254913, AW875172, AI281689, AA668587, AA084619, BF675051, AI354423, AA832077, AI733129, BF674550, AL041924, BE139451, H73550, AA828853, N39953, AW863393, AV757526, AI859946, AW976008, AW023111, AA747234, AI565084, AV710482, AW814024, AV710045, AW963482, AI355246, AA814925, BE077105, AA653182, AA664521, AW440305, AI054397, AA651639, BF725761, AV758073, H15652, BE280771, AW438542, T74524, AW191063, BF940118, AW968205, AV762973, AA552578, BF965924, BF879045, AI251034, AI251203, AI251284, AW805539, BG236628, BE878259, AI250552, AA632556, BF809041, BG029224, BF868994, AW020736, AF236698, BE139139, AW271904, BF978025, BF681424, AU118374, AV758790, BG110480, AI803809, AV758097, AA574442, AV733434, BE155302, AA644664, AI792521, BE246472, BE901278, AA626825, AI686913, AV706237, BE155299, AW302293, AV702609, AA533123, BE968477, AV738383, BF814446, AI891080, AA516190, AA533040, AI284543, BE273825,



				<p> AW779609, BF525663, AI380617, BF914419, AL079734, BG166965, AW069227, AL043351, AI267161, AV762870, AV658819, AV709273, AL042735, AA503018, AI973173, AL046746, BE062357, AI963705, T69857, AV730245, BF810071, AW301736, Z97987.1, AC020913.6, AL031281.6, AC007637.9, AL096757.1, Z93017.6, AC087225.1, Z83840.7, AC008073.4, AF245699.1, AC010349.7, AC087315.21, AL163011.3, AC004106.1, AC004132.1, AC008925.3, AC004990.1, AL133351.33, AC010618.7, AC006275.1, AL035405.10, AC034203.7, AC006930.1, AF156495.1, AC008754.8, AP001732.1, AL139824.22, AC003037.1, AP001646.4, AC005162.1, AL050341.18, AL034420.16, AC024075.4, AL117382.28, AC008521.5, AP001039.1, AL512378.7, AC005778.1, AC091394.2, AL132768.15, AL139385.12, AL049569.13, AL109914.16, Z95152.1, AL163541.13, AC006367.3, AL442203.12, AC005684.1, AL117377.18, AL109828.22, AL031681.16, AC007488.15, AC007425.16, AC018462.4, AC007934.7, AL078602.13, AC010002.6, AC005038.5, AC009743.1, AC006538.1, AC053467.1, Z95115.1, AP001922.4, AC010203.13, AC010150.3, AC006545.3, AC006546.9, AC004970.2, AP001696.1, AL390736.6, AC003035.1, AL355543.13, AC007318.4, AC007381.3, AC006253.4, AC022173.7, AC040160.4, AC003684.1, AC009331.5, AL109823.23, AL451107.6, AL359873.11, AC004605.1, AL035682.16, AP002453.3, AC063947.30, AC006270.1, AC016526.6, AC003664.1, AL078634.24, AL157897.7, AL009031.1, AL137802.7, AJ251973.1, AC002326.1, AL356421.10, AC006388.3, AC078846.2, AL138721.16, AC004103.1, AC090949.1, AC090944.1, AL139150.12, AL162423.18, AP001718.1, AL109915.10, AL390208.17, AC004616.1, AP002851.2, AC017100.4, AC022425.6, AC006080.1, AC005027.2, AC017006.4, AC024163.2, AL049540.11, AC005522.2, AP000353.2, AC008008.2, AL445205.14, AC078843.2, AC073864.28, AL161657.22, AL031280.6, AL035696.14, Z81364.1, AL157938.22, AC090426.1, AL389883.9, AL024474.1, AL138703.10, AC008266.3, AC073057.6, AL132800.4, AC007784.7, AC002996.1, AL354816.5, AC011449.6, AP00193.1, AL022313.1, AC008379.6, AP003355.2, AC005004.3, AC005514.1, AL118501.22, AL009028.1, Z86064.1, AP002812.3, AL035249.6, AC009131.6, AC002549.1, AC032011.14, AL109984.14, AF001549.1, Z84467.1, AL034419.22, AL512883.5, AC006204.1, AL353574.8, AC006960.1, AC009079.4, AC009503.3, D87009.1, AL354932.26, AC005014.1, AC005859.1, AL139110.17, AC003662.2, AL035089.21, AC005751.1, AL390738.4, AL133246.2, AP000694.1, AC020659.5, AL133355.12, AC004854.2, AL359236.4, AC006237.1, AK023233.1, Z85999.1, AL022323.7, AC003046.3, AL031730.1, AL160471.5, AL160071.16, AC010548.8, Z82206.1, AF029308.1, AC005498.1, AL133342.14, AP000348.1, AC011465.4, AC004812.1, AC007221.2, AL022316.2, AL035072.16, Z97630.11, AF312032.1, AC008551.5, AC007685.2, AC005034.1, AL391602.6, AC005220.1, AP000117.1, AL023883.6, AP001150.4, AL109825.23, AL137782.9, AL096800.20, AF252279.1, AC005695.1, AC016993.4, AC007620.30, AL022237.1, AC006481.3, AC018812.5, AL035420.15, AC004611.1, Z84487.2, AC018719.4, AC010163.7, AL133344.28, AC011290.3, AC007292.1, AC011895.4, AP001929.4, U63721.1, AC002352.1, AC011444.5, AC005327.1, AL451075.15, </p>

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HFKFG02	95	634743	1 - 781	15 - 795		BE222940, AI479528, AW242860, R46796, M62053, AI017670, BE048467, AI671740, AW001738, AA351031, AI206414, AF124373.1, AB009698.1, AF104038.1, AB009697.1, AF057039.2, AP001858.4, AJ249369.1, AF097490.1, AJ251529.1, AJ271205. 1.
HFTBM50	96	545012	1 - 748	15 - 762		AL529436, BG254023, AA069656, AW512689, AA928735, BE901109, AL529437, BE074967, BE074973, AA423996, AI027673, AI130940, AA827360, AA424006, AA421599, AW602733, AI580837, AL526924, AA114876, AA576953, AI858981, BF222157, AL526960, BF542049, AA136831, AI200715, AI358322, AA988755, AW602739, AA187921, AL527090, HI0340, AI499041, HI0044, AA252300, AA188494, AA856927, R44331, AA588683, AW364266, BE092940, BE007334, R51006, AI253378, AA481649, AI686745, AI628242, BE092920, BF733881, AA729977, BF026424, AW804569, AA421594, AW994967, AA481416, BE733257, BF876214, AA679567, AW028221, AU134538, BE251492, BE729280, AI906091, BC002480.1, AK023414.1, AP002347. 3.
HFTDZ36	97	545726	1 - 1089	15 - 1103		AV721599, BF732420, BF510533, BF508158, BF508241, AI638188, AW181935, AI758929, AW592730, BE967495, AA447514, AI078837, AV723652, AI218418, BF692673, AA884756, AI335250, AW118870, BE044339, AA426363, AV730822, AI868197, BF947599, AA927228, BF952754, BF952302, BF952504, AW905268, AW905266, BF952591, AI673798, BF952850, BF952505, AW905263, BF952750, BF952589, BF952851, BF952752, AA897687, BF572515, AW905328, BE699539, AI830527, BF952755, BF210822, AA431528, AA029326, H41714, AA437157, N53641, BE699547, AW905379, BE699537, BE796741, AW898982, AI218421, AF289076.2, AC067967. 2.
HFXBL33	98	778070	1 - 1619	15 - 1633		BG141322, AV652809, AV662223, AV699247, AV699167, AV662247, AW963961, AV699098, AV662272, AV725496, AV727824, AV699218, AV719825, AV719156, AV699200, AW952432, AV720062, AV720893, AV653163, AV650903.
HFXHK73	99	609826	1 - 1859	15 - 1873		AP001741.1, Z49918.1, AP001610.1, AC009399. 5.
HFXIX44	100	701988	1 - 1370	15 - 1384		AC004491.1, AC024579.4, AL136084.11, AC016564.5, AC005015.2, AC007011. 1.
HFXKY27	101	634161	1 - 931	15 - 945		AA483223, AA552843, AV762050, BF991286, AA623002, BF827410, AW193265, AI434706, AV759204, BE350475, AI270117, AV760937, BF217299, AV710066, AA610493, AI350211, AL041690, BF475381, AV764241, AV764307, AW673241, AV762139, AI192631, AA552856, AV763540, BF676536, AA468131, AV682003, AI368256, AI345157, AA649705, AI345518, AV760774, AA480772, AA521323, AI538433, AA644538, AL037683, AA577906, AA613227, AA503475, AW270382, AI355206, AW021583, AV759274, AA521399, AV761155, AA492166, AV735495, AI431303, AA490183, AW088846, AF330238, AA857486, AA493621, AV759382, AW438643, AA579362, AI610159, AA525790, AA507824, AV742057, AV763255, W60061, AV761786, AA644551, AI254615, AV735370, AW872676, AA649642, AA652057, AA984708, AA579736, AA682912, AA525824, AW238583, AW977303, AA470969, AI963720, AV734666, AV760624, AV762826, AA970213, AA908422, AI613280, BG150790, AV760777, AA834755, AW513362, BF668217, AA657535,

				AV761925, AA357937, AV730301, AV763971, AA491831, A1688846, AW731867, BE502107, AW517737, AV762558, AW238542, AA766151, AA862173, AA350859, A1619997, AA501418, AV702857, AA601355, A1634384, AF001552.1, AL354749.6, AL122015.17, AL163032.3, AF279660.2, AL034405.16, AL035699.4, AL365315.8, AC010269.5, AL022163.1, AL031661.28, AC090497.2, AC005084.1, D83989.1, X55926.1, X54181.1, U57007.1, X54178.1, U18391.1, U18392.1, U57006.1, U18394.1, X55925.1, U57005.1, X54179.1, X75335.1, X55932.1, AC020728.4, U18390.1, AC004887.2, M37551.1, X54175.1, U57009.1, U18395.1, AC006511.5, U18393.1, X54176.1, U57008.1, AC005521.1, AL135903.12, AC004662.1, AL158052.10, AC004525.1, X55923.1, AL136090.12, AL157955.5, Z22650.1, X54177.1, AL133332.12, AP001677.1, U18400.1, AC009481.4, U18396.1, AL121891.22, U18399.1, U57004.1, AP001696.1, AC002529.1, AC009950.6, AC005740.1, AL049745.9, AC006287.1, AC009498.3, AC034305.6, AC008168.3, AC004972.2, AC011938.4, AL031275.1, AC008962.8, AL139350.17, AL590621.10, AL050325.20, AC005913.2, AC010748.5, AL109755.14, AL157830.10, AC002303.1, AC009508.3, L47228.1, Z77249.1, AP000501.1, AC073138.3, AC006376.2, AC010482.7, AL049563.4, X55927.1, U18398.1, AC005274.1, U18387.1, AL139082.18, AL049539.21, AL138721.16, AL359393.9, X55930.1, AC008766.4, AL023281.1, AC009802.13, AC027345.4, AC002115.1, AC007272.3, AC008109.6, AC017078.8, AP002392.3, AL355578.4, AC018637.3, AL049713.20, AC004622.1, AP001700.1, AC009779.18, AC005158.3, AL162587.20, AF117829.1, AL163278.2, AC087312.8, X74558.1, AC007934.7, AL499604.9, U67831.1, AL354869.11, AL161935.10, AL589988.6, AC022335.8, AC022407.6, AC073910.20, AL356796.16, AL133415.12, AC008134.3, AL354751.7, AC016080.5, AL391478.14, AC011310.3, AC005544.1, AC005297.1, AC013264.4, AC003010.1, AC004491.1, AC002128.1, AC009311.3, AP001727.1, AL163248.2, AC087600.21, AL359012.7, AL022162.1, AL354716.9, AC022740.4, AC090886.1, AJ011930.1, AC090004.1, AL050333.18, AL590762.1, AC012410.9, AC009623.6, AC002091.1, AJ006995.1, AC006128.1, AP002532.1, AP003467.2, AC007970.3, AP000555.1, AL138759.20, AC012315.5, AC007179.3, AF149773.1, AL049613.2, AC008071.2, AL359380.16, AL354668.13, AC007132.3, AC084882.2, AC090710.16, AP002812.3, AC013242.7, AP002906.2, Z72001.1, AC004806.1, AL133344.28, AF195953.1, AC004865.1, Z92844.1, AP001533.4, AC004047.1, AC006375.4, AL137077.31, AL445663.10, AL133472.12, AF188030.3, AP002007.4, AL031390.4, AC008268.3, AP001683.1, AC008482.5, AC003983.1, AC017004.4, AL449265.13, U67829.1, AL109823.23, AD000090.1, AP000472.2, AP002026.1, AC016716.6, AL135786.17, AL353691.12, AC005399.19, AL020994.1, AL353800.10, AL158210.12, AP003438.2, AC016763.8, AC020698.4, AL357515.26, AF246928.1, Z94044.1, AF227510.1, AC008543.7, AC018809.4, AF077058.1, AP000567.2, AL357141. 8	
HGBH135	102	570262	1 - 1423	15 - 1437	AW027617, AW167655, AV705616, BF112047, AV647323, A1761852, AV647362, BF475491, BF941241, AU134617, AW273477, AA632135, BF589834, AW188958, BE328783, BF673582, AW025350, AW469123, A1248475, AW071025, AW513405, AV707439, AA443956, AW959532,

					<p>AA974499, AA586906, AA411210, AA748561, AV647324, AA574049, BF001545, AA993212, AU155540, AA405832, AA418055, T65000, AA633212, AA417996, AA716696, AW338423, AI951713, AW269824, AA705781, AW294610, N29931, AW193961, W74344, AI623473, W95062, N58311, AA434443, AI452555, AI476814, AI707848, AI591113, AW071570, AA504192, AI284330, AA993753, AA422102, AA814543, AA833607, R59175, H69589, N27730, N27744, AI050821, H91466, AV661353, N26927, AA384582, T53881, AA723025, AW952885, AA708478, AA412129, N80150, AA805411, AA325056, H86073, AW080735, AA719996, H48787, AW439101, AA327279, AW439110, R72184, AA317298, AA290758, AI302593, AI041429, AA932990, AV692965, H68481, AA290757, AI301278, AA928847, AV709914, R70407, AA342345, AW971285, T71152, AA528307, R00838, AI915200, AI470398, AA888272, T50944, T54028, AI784177, R69430, AI298655, AI801093, AA363967, AA935078, AA935062, T99499, AW450038, F37718, AI470409, AA419235, AW074842, AA700546, BF057503, AV656088, AI798643, AA946561, AV684912, C05231, AA342344, AA405831, AI682312, R72230, AV696820, AI557037, T72850, BG122003, AI478342, AA504193, AI474859, W91943, BG164862, AW841423, AI243763, AI364219, AA879063, AA419337, AV698254, BF847168, BG004190, AK001810. I.</p>
HGLAF75	103	566838	1 - 762	15 - 776	<p>AW968403, AW268460, AV699333, BE388094, BE387809, AA805707, BF112044, AA769677, AI379717, AI419895, AI858342, AI708860, AA044030, AA465222, AI677780, AI189447, AI221144, AI073526, AI286149, AI540808, AI298414, AA847808, N29749, AW170779, AA344901, AA044352, R52970, BE836466, BE716265, BG057223, BE836496, H40701, R55340, AA873679, AI363753, BF792412, R40137, AW965142, AA725486, AA344902, T27542, BE716174, N57171.</p>
HHBCS39	104	1003028	1 - 2881	15 - 2895	<p>AU118319, AU118145, AA001321, AI268416, AU144910, AA004368, AW291988, AU144790, AA677418, AI056605, BE708494, AA001908, AA707413, AA903931, AA004369, AA122399, BG000061, AA152481, AA878867, AV695708, AA152372, AI279749, R28072, AI446406, AI565299, T82947, R28288, AA346924, T97751, T97858, AI242583, AW839578, AK024922.1, AK021612. I.</p>
HHEAA08	105	638231	1 - 2136	15 - 2150	<p>AL520596, AI370425, BE567612, AI343143, AI016704, BF678494, AI284640, AI952900, AL038606, AW302048, AI049996, AW500125, AA318267, BE139267, AW979140, AA484143, AV763401, AW021774, AI345123, AW302315, AI754661, BF725347, AV762129, AL039187, AL079734, AI344810, AV763657, BE676900, BE139358, AL045077, AA192278, AW069227, AV710066, AV758989, AL526288, AA528480, AW303196, AW088125, AI270117, AA491814, AW301350, AA448838, AI538812, AL041706, AI918013, AV682003, AI754291, AU154948, AV760937, AW419262, AV728928, AW833862, AW731867, AW238016, BG031290, AI696793, AA524832, AA601680, BF926429, BF916934, AI473701, F32710, N91310, AA730635, AI634187, AW193265, AW504224, BG033217, AA167055, N22032, AV755512, AL046409, AC016601.6, AL121988.10, AC010219.4, AF235097.1, AL035450.1, AL132986.4, AL133260.12, AC004000.1, AC005291.1, AL031431.8, AC009087.4, AF130343.1, AL138880.14, AC007036.3, AL132987.4, AL031719.12, M69197.1, AE006467.1, Z85996.1, AC012076.4, AL035400.13, AC007564.9, AC006206.3, AL449212.1, AL158830.17, AL356378.17, AL049569.13, AL031584.1, L78810.1, AL121845.20,</p>

				AC007566.2, AC011465.4, AC005540.4, AC025572.13, AP001713.1, AC002352.1, AC007193.1, AL139092.12, AF001549.1, AL121865.7, AC010458.5, AL121895.26, AL133415.12, AL121657.2, AL389921.12, AP000100.1, AL031727.42, AL161747.5, AC008395.6, AL353140.12, AC073593.13, AL157828.14, AL157398.6, AC079141.7, AC006952.6, AL034431.16, AC078962.30, AC008882.6, AC009228.4, AP001694.1, AL121899.37, AC005697.1, AL160273.9, AL031291.3, AC008745.6, AL137859.3, AL161896.16, AC007055.3, AL121910.26, AL117328.5, AL450169.1, AC005768.17, AP000208.1, AP000130.1, AC005071.2, D83989.1, AP002008.5, AP000247.1, AL353613.10, U95740.1, AC002045.1, AC006057.5, AC009314.4, AC008747.5, AF279660.2, AC004231.1, AC078961.23, AP001725.1, AL035089.21, AP003357.2, AJ003147.1, AL359739.8, AL352984.4, M55538.2, AC005304.1, AC079045.2, AC004522.1, AF241728.1, AC007221.2, AL161937.13, Z82097.1, AF069291.1, AL110114.1, AC008482.5, AL109615.41, AL391122.9, AC018618.5, AL161421.11, AL049869.6, AC010489.4, AC005007.1, AC083870.2, AC006285.11, AL158035.14, AC007198.6, AC078876.15, AF243527.1, AL391280.15, AL031681.16, AC016025.12, AL160410.24, AL138762.20, U93305.1, AL031985.10, AL121754.18, AC008394.3, AC007161.1, AL590732.7, AC022212.4, AP002851.2, AL356321.9, AL008708.4, AL359846.11, AC006270.1, AL050349.27, AL445483.13, AC005325.1, AL353748.13, AC009955.4, AC002381.1, AL122004.17, AC009230.3, AL049776.3, AP001710.1, AC008547.5, AC008555.5, AC005520.2, AC002565.1, AL031176.8, AL138741.13, AC005678.1, AC004590.1, AL133551.13, AC009238.4, AC007673.7, AC008872.5, AJ289880.1, AL096793.20, Z85987.13, U57009.1, AC004890.2, AC005822.1, AL590762.1, AL160237.4, AL391684.6, U91326.1, AC083875.1, U96629.1, AP000426.3, AC013429.12, Z98051.6, AL031055.1, AL049758.11, AC004826.3, AL355096.4, AC009309.4, AP001830.4, AC008755.6, AC007749.3, AC005887.3, AC002395.1, AC002418.1, AC010504.7, AL161627.13, AL118511.25, AL139317.5, AL442203.12, AC004386.1, AP001972.4, AC016830.5, AC004832.3, AP001614.1, AC004846.2, AL035685.21, AC005701.1, AL132713.11, AC007465.4, AC005669.1, AL352976.3, AF134726.1, AC006052.5, AL133328.13, AC079684.16, AC011739.7, AC016027.15, AL359851.19, AC078958.30, AC022173.7, AC011359.5, AC006026.2, U57007.1, AL139100.9, AL445675.9, AL445258.4, AC009470.4, AL133324.13, Z82194.1, U18391.1, AC002316.1, U18394.1, AL356801.5, X54176.1, AP001781.4, AL135907.21, AL353734.12, AL031963.40, AL133338.8, AL135744.4, AL121601.13, AL359813.23, AP000036.1, AC009464.7, AC004812.1, AC018710.4, AL160192.3, AC026463.4, AL109825.23, AL121902.13, AC019041.8, AC079602.15, AC004912.1.
HHENV10	106	562772	1 - 1141	15 - 1155
HHFFJ48	107	634521	1 - 2552	15 - 2566
				BF72051, BF760479, AA486028, AL536141, N91095, AW301931, BF772459, AW852705, AW852684, AW852657, BE138714, AB058744.1, AL589723.7, AC006512.12, AL451107.6, U47924.1, AL590762.1.
HHFHJ59	108	411332	1 - 647	15 - 661
				AA833770, AW877426, AA804902.

HHGBO91	109	520198	1 - 701	15 - 715	AA363260, AW063936, AI343123, AI648433, BE386324, BE409452, BF793428, AV738722, AV740060, AI284640, BE139358, AI612152, AL046409, AI254798, AV756074, AV712125, AV756848, AI061313, AW965518, AI284881, AI284888, AV757334, AI890348, AV760395, AI612032, AW303196, AI963720, AW301350, AV725431, AI306232, AW021774, AW021917, BE252421, AU152795, AV710482, AW274191, BE744242, AW274349, AW962942, BG249643, AI251576, AI583466, BF678427, BF980463, BF243118, AW504022, AW501806, AL048255, AV682003, AI254540, AI224184, AA747889, AW504104, AI349748, AI275328, AI251250, AW504480, AF074677, AI311505, AI064864, AA744001, AI610603, AI801205, AA572992, BF337291, H98660, BF673630, AW238583, AI053786, AA496901, BF917533, AI138455, AI590522, BF325535, AW499745, AW961593, AP002347.3, AC011475.6, AC004150.8, AC005231.2, AC005368.1, AL139100.9, AL096840.25, AF196969.1, AC007314.3, AC008760.6, AL132780.5, AL034372.33, AC016587.7, AL133163.2, AL133517.11, Z83826.12, AC005280.3, AL163032.3, AC019205.4, AP001716.1, AF111168.2, AC090939.1, AL096701.14, AC004965.2, AC005520.2, AP001726.1, AC004983.2, AJ400877.1, AL022476.2, AC006480.3, AC011464.5, AL096791.12, AL022326.1, AC006285.11, AC004638.1, AC007664.12, AC005701.1, AC008403.6, AL139809.16, AL139316.5, AC021999.4, AC005052.2, AC073657.5, AL121655.1, AC018711.4, AC007256.5, AL445483.13, AL137792.11, AL035683.9, AC004815.2, AL138849.12, AC011446.6, AL035587.5, AC003982.1, AL049761.11, AC004166.12, U95090.1, AC010530.7, AC000052.16, AC010319.7, AL139376.17, AC020754.4, AL356214.20, AC084865.2, AF254822.1, AC016772.8, AC083866.2, AC008946.6, AC004755.2, AC007386.3, U91321.1, AL049776.3, AC005089.2, AC011742.3, AC018808.4, AL033529.25, AC009086.5, AC002425.1, AC005736.1, AC005291.1, AC020928.6, AP001727.1, AC044797.5, AL360169.17, AC006530.4, AL355385.15, AC003070.1, AL031727.42, AL109797.18, AC007374.6, AC005295.1, AC006345.4, AL035458.35, AC006483.3, AC007114.7, AL450226.1, AC040160.4, AC008806.4, AC009501.3, AC007172.6, AC004148.1, AC008521.5, AL022336.1, AC008440.8, AC006001.2, AL135978.4, AL109743.4, AC008622.5, AC004033.3, AC024561.4, AC004475.1, AL139415.10, AP001728.1, AC020915.6, AC011465.4, AL139113.21, AC022007.3, AL080242.11, AL121652.2, AL049539.21, AC009060.7, AC008738.6, AL050335.32, AC027319.5, AL355392.7, AC007766.1, AC011484.4, AC021016.4, AL049569.13, AC012476.8, AC010311.8, AL035405.10, AL031005.1, AC004019.20, AC002565.1, AL031597.7, AC005971.5, AC079602.15, AC006064.9, AC005288.1, AC005015.2, AC002470.17, AL451125.7, AL008721.1, AC005077.5, AC006330.5, AC010326.6, AC034193.4, AC006329.5, AC008482.5, AC073138.3, AL162426.20, AC015982.9, AL353748.13, AC002310.1, AC016831.1, AC005844.7, AC007878.2, AL050349.27, AC006441.13, AC021188.6, AC004417.1, AC008280.4, AL137852.15, AC022392.4, AC007421.12, AP002812.3, AC069223.15, AC007686.5, AP001331.1, AC018758.2, AF107885.2, AC004971.3, AL132640.4, AC018828.3, AC074013.5, AL049780.4, AC007308.13, AP003357.2, AC010677.4, AC002316.1, AL031230.1, AL109628.5, AL008627.1, AC009570.13, AL512378.7, AC007255.4,
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HHGCM76	111	662329	1 - 697	15 - 711		AW248957, BF828801, BF828604, AI675194, AW028119, BF826770, BF827069, AW452880, AI491913, AI799880, AW450970, AI377883, AI201976, AA595164, AI088096, AW612440, BE792795, AW006952, BF063362, AI697133, AA643065, AA580017, AI819005, AI866931, AI560641, AA635584, BF446220, AI829011, AW952316, AL524066, AW243832, AI200458, AI634449, AI670745, AI269568, AA326815, AI873666, AL523219, AL520944, AI478177, L31980, AW245254, AW194690, AW771866, AI767850, AW079488, T87766, D45523, BE242113, AA055697, AI306732, AW275312, BE280419, AI908657, R48473, AA013188, AI908646, BG250796, BE796614, T72628, BC002980.1, AC003665. 1.
HHGCQ54	112	544615	1 - 861	15 - 875		AL528163, BG252074, BF529806, BF855582, AA234290, AW264333, AI122942, AW293770, AA458524, R41805, AW338445, AW264239, AI091253, AW316552, AA454605, AI459366, BE299516, BF856403, R42539, AI698643, AI082503, BF436761, AI673224, AI864282, BG222925, F11117, AW293131, AI446586, AW029153, AA568555, AI123718, AI352145, AA234190, BG251585, AI459970, R41441.
HHPEN62	113	695134	1 - 2138	15 - 2152		AI939620, AI480056, AW300615, AW300620, AI589129, BE386438, BF920454, BE386547, AW961851, AI911546, AV726263, AI361251, AI498527, AV725146, AW901919, BE967591, H41544, AA326679, AA348503, AI422476, AA912288, AI423129, BC004271. 1.
HJABB94	114	456466	1 - 1541	15 - 1555		BE905356, AI026821, AA503776, BF114724, AI435527, AL036946, AW298357, BF240642, AA969442, AI767392, AI142574, AI094514, AW073866, AW241144, AA206595, AA040034, AA354909, AW972134, AA814156, AA933895, AA040828, C01416, AA457220, AL138875.8, AY027525. 1.
HJACG02	115	1307789	1 - 561	15 - 575		AA311223, BF002026, N41594, N30820, BF982046, AI829327, BE047833, AI457369, AW071417, BF968205, AI340627, R36271, AL036980, BF061283, BG168549, AW022682, BG034550, AV682418, AL047042, BF343172, BG113299, AW020693, BF751308, AI452560, AI690748, AI349645, AW946806, AI340511, BF924882, AW074869, AW196299, AL038445, BE781369, AW302992, BG110684, BE887488, AL514193, AI310575, BG164558, AI340533, AI349957, AI433384, BF680133, AV715560, AI309401, AI345005, BG163618, AI343112, AV743962, AI826225, AI811785, AI494201, AW054931, AW268302, AW301300, AI349598, BF672397, AW072719, AW075207, BF526020, AV741327, AI345735, BG036846, AI697243, BE536058, AW193134, AI889147, BF904189, BE910373, AI500077, AA225339, BE138712, AI307210, BG033723, AI589267, AI269862, BE885353, AI313320, BG058150,

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HJACG30	116	895505	1 - 1518	15 - 1532	<p> AL162002.1, AB048964.1, AL133080.1, AL390154.1, BC006164.1, AK000137.1, AK026762.1, AL117460.1, AK026630.1, AL512689.1, AL512719.1, AL050108.1, AK026593.1, AB063100.1, S61953.1, AL049300.1, AL049452.1, BC005151.1, AK000647.1, BC001045.1, AB063079.1, BC002733.1, AL136893.1, BC002342.1, AK025383.1, BC004556.1, BC009284.1, AL080086.1, BC005678.1, AF078844.1, AF026816.2, AL136928.1, AL512750.1, BC003627.1, Y16645.1, AB062942.1, AF051325.1, AL512754.1, BC006103.1, U58996.2, AB060863.1, AL136844.1, AK000212.1, AL080074.1, AL359601.1, AF262032.1, AK026600.1, AL136864.1, U80742.1, AL136845.1, AL122093.1, BC008893.1, AL136892.1, BC006201.1, AL117435.1, BC008365.1, AL110280.1, AF061943.1, AL136749.1, AK027868.1, AB019565.1, AF162270.1, BC008382.1, AL133104.1, AF003737.1, AF353396.1, AL137557.1, AK000445.1, BC008284.1, AK000432.1, AF218014.1, AL136786.1, AB050510.1, AK024601.1, AL117583.1, AL137648.1, AB060929.1, AK025491.1, AL117585.1, AL122098.1, AK025573.1, AF219137.1, AF090903.1, AF125949.1, AF260366.1, AL050146.1, AF111847.1, AL442072.1, AB062978.1, AJ006417.1, AL122121.1, AJ012755.1, AL136784.1, AF104032.1, BC008488.1, AL080060.1, AB055315.1, AL137478.1, AB047887.1, AF132676.1, AF061836.1, AF183393.1, AK027204.1, AL080127.1, AK026647.1, AK027116.1, AL096744.1, AB055361.1, AL353940.1, BC008387.1, AL137556.1, X82434.1, AF090934.1, AL122049.1, AL162008.1, AB063070.1, AL122050.1, AL162003.1, AL137271.1, BC005168.1, AB048974.1, AK025798.1, AB055368.1, S78214.1, AK000486.1. </p> <p> AA311188, BF940968, AI478697, AA309875, AA481249, AL533052, AA481563, AW242463, AA760629, AV651897, AV660258, AV661286, AV709580, AV653353, AV726590, AV703632, AV725255, AW960067, AV705453, AV726243, AV652001, AV704144, AV726194, AW956292, AW949777, AV708520, AV727618, AW959858, AV656283, AW967329, AV727932, AV728953, AV725582, AV708786, AV708872, AV661369, AW952013, AV705340, AV704234, AW965148, AV726156, AV705836, AV708991, AV725618, AW952301, AW958796, AV725596, AV709248, AW959986, AV726337, AV709407, AV728355, AV725031, AV707948, AV725441, AV729424, AV652528, AV725577, AV707556, AV704626, AV702071, AV706223, AV705665, AV704785, AV728404, AV709733, AV729366, AV708320, AV705343, AV727822, AV707264, AV704611, AV729473, AV702738, AV725321, AV690930, AV728743, AV727978, AV727337, AV727562, AV729129, AV704712, AV701953, AV727052, AW955629, AV729532, AV704520, AV706964, AV704973, AV702817, AV705504, AV709356, AV704279, AV705829, AV702164, AV701880, AV701626, AV707401, AV704756, AW955019, AV701183, AV728289, AV708203, AV703591, AV697880, AV647941, AV703417, AV753624, AW963446, AV654035, AV709935, AV726628, AV707654, AV706290, AV655552, AV654282, AW949521, AV709880, AV709939, AV705189, AV704686, AV706882, AV727314, AV702954, AV727238, AV691615, AW967328, AV682997, AV727126, AV727347, AV728652, AV702787, AV706162, AV709596, AV686417, AV701728, AV701873, AV656240, AV692972, AV694871, AV705239, AV727459, AV655901, AV728715, AV701499, AV703972, AV703090, AV707794, AV702790, AV728546, AV705267, AV703762, </p>
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HJBCY35	117	719729	1 - 1545	15 - 1559	<p>AL518865, AL526445, AL518864, BF690211, BE795952, BG261247, BG122941, BE871131, BF342499, BF797882, BG034854, BE874386, BF684303, AW958340, BF055513, BE265238, BF055496, AL042954, AL044311, AW393087, BF590235, BE251517, BF688851, AW500006, BF750912, BF436031, BE207255, AI523943, AI809559, AW615714, AI088845, AI199469, AI088821, BE792741, AA707004, AI393362, AI859578, AA864359, AI359119, AI963339, AA259086, AW027379, AA186786, AA703021, AA305929, AA393356, BE729570, AI961726, AW274049, AI216448, AW503180, AW505339, AI015694, AA291342, AI049539, AW873566, AI092749, BE410341, AI817912, AI870620, H44330, AI366215, AA258242, R46300, RI6949, AI744596, R54656, BE386449, BE410337, AI807057, AW081887, AL041401, H15972, BE710574, BE410414, BE535502, BE222788, AA398688, AW273864, AA404987, D59795, AA077661, BE047327, T10451, AI871075, D59810, AI368575, BF526818, AA962247, AA335735, AW000813, BF435172, AA188015, R75708, AA329264, BE713106, AI218840, AA329538, AA291343, AA826970, T35806, R10855, D59833, D59821, BE547124, D80231, AI080034, AA299767, BF203222, AI908002, AA973311, AW087244, BF920764, AI648592, D80329, BE537114, BF511965, D59677, W93021, AI919083, AA749327, R16895, R55419, AA354448, AA136776, R54853, R46205, D59561, AI969256, W51754, AW273865, R10856, AI452772, BF765954, R10335, BF858687, AA076725, BF955782, BF206768, BF310354, BF032473, C01203, BC004286.1, AL050110.1, AB037861.1, AL137358.1.</p>
HJPAD75	118	651337	1 - 1217	15 - 1231	<p>AL530365, AL524811, BG035149, AL524846, AV653215, AL525028, BF031163, BE464161, BF064198, BG057645, BE677690, AV714679, AI954819, AA708718, AA773040, AW206827, BE677490, AW590005, AL522800, AI075390, BG179367, AI933314, AA022693, AA563665, AI582700, BF591973, AI933036, AA011394, BE463890, AI304827, AW467513, AI675049, N47573, BE537595, AI075392, AI346305, AL514603, W26975, H02832, AI290715, AA535130, AW137781, AW298065,</p>

HKABZ65	119	862030	1 - 1175	15 - 1189	BF927479, AA917670, AA011431, AL530366, AA974770, AA535120, AI497684, AI277012, AI274193, AL514604, AW297638, AW779938, AA356778, AW067366, AL524812, AL524847, BF763877, AV652546, H03723, F09604, F09318, H83110, AA216050, AW573003, BF926201, AI572540, AL525029, BF092250, D80466, AI940747, AK027129.1, BC008984.1, AF043945.2, AL163284.2, AA715814, AA503019, AV762033, BE155099, AV734997, BF917346, AW338860, AC011666.28, AF242518.1, AF109907.1, AC004867.5, AC020917.4, AC004166.12, AL356915.19, AC005071.2, AC004878.2, AC005052.2, AC005081.3, AC002549.1, AL590763.1, AC020663.1, AC006064.9, AC008745.6, AC004858.2, AC022405.5, AC007666.12, AC008750.7, AL451144.5, AP001716.1, AC009131.6, AC004656.1, AL109825.23, AL355312.24, AL035086.12, AC010605.4, AC004067.1, AC004477.1, AC008736.6, AL109915.10, AC006023.2, AL033529.25, AC007637.9, AL139317.5, AL031311.1, AL049776.3, AC004971.3, AC009220.10, AL080243.21, AC005015.2, AC004686.1, AL022318.2, AC002310.1, AC009123.6, Z93015.9, AC021999.4, AL355353.23, AL050318.13, AL161756.6, AC011464.5, AL132712.4, AL359513.12, AC007546.5, AP001695.1, AL035683.9, AC018711.4, D87675.1, AL133444.4, AL139100.9, AF030453.1, AC006077.1, AC008895.7, AP001713.1, Z84487.2, AL357153.4, AL163636.6, AL359382.23, AC004770.1, AP001972.4, AC004675.1, AL355392.7, AC020906.6, AL138784.30, AC020754.4, AL162426.20, AC002288.1, AC009068.10, AC008101.15, AC008623.4, AC008891.7, Z98884.11, AL136137.15, AC011247.10, AL133163.2, AP001727.1, AC005098.2, AC004659.1, AC005670.1, AL139022.4, AC009812.17, AF088219.1, AL035404.20, AL139801.17, AF228703.1, AC002492.1, AC006084.1, AL353594.13, AC005077.5, AL160271.19, AP001724.1, AC008537.5, AC024561.4, AL139353.3, AC004491.1, AC008626.5, AL391987.15, AC010530.7, AP003352.2, AC009267.15, AL122013.5, AP000008.1, AC087071.2, AC009314.4, AC020913.6, AL078463.11, AL096700.14, AC002369.1, AC010102.3, AP003357.2, AL031123.14, Z95331.2, AL513008.14, AL118501.22, AP001435.2, AC005200.1, AJ400877.1, AC011469.6, AC016772.8, AC005089.2, AC005088.2, AF312912.1, AL022316.2, AL080317.11, AP001693.1, AP000553.1, AL390294.19, AC006345.4, AC091394.2, AL359813.23, AC007283.3, AL353807.18, AL109921.21, AC074121.16, Z98742.5, AC007383.4, AF243527.1, AC027130.5, AC010504.7, AL035462.21, AC010650.8, AC005180.2, AF334404.1, AL139187.19, AC005037.2, AL021391.2.
HKAF766	122	946512	1 - 987	15 - 1001	AA436785, AI804932, AA310516, AW966935, AA873013, AA251417, AI798761, AA250867, BE720668, AW827206, BG122481, AI826225, AI811785, AI539808, BF970449, AL039086, AW983783, AI554821, AI784252, AW105601, AV708119, AW054931, AV727839, BF968205, AL119863, AI280747, AI611738, BE047737, BF970768, AW193134, AW118518, BF904265, BF089711, AI610362, AL042628, BF793370, AL036980, AI312428, AA833760, AL513763, AI829327, AI433384, AI589267, AI269862, AI564723, BG031539, AI624548, AW302992, BG260037, AI802542, AI569583, AW169653, AI800453, BE048071, BF792961, AI439717, AI567612, AI611348, AI869367, AW081797, BF343172, BG031815, AL038605, AI570781, AW051258, AL513901, AI802240, AI274728, AW071417, AI571909,

				BG249582, BG257535, AW152469, AI612885, AW022682, AW148320, AI569579, AI252023, AI608936, AW075413, AI500077, AI318280, BE781369, AI636585, AI251434, AI862144, BG255895, AI890806, AI625094, AI955906, AI309401, BG110517, AI431424, AI343112, AI612913, BG110684, BE895003, BG168549, AW268253, AW301300, AI349598, AI554344, AL036664, AW075207, BE886728, AI345735, AI678357, BE964078, BF872670, AI475394, AI633419, AI348897, BF904258, BE138712, AI500659, BE966699, AI247193, BE887488, BG030364, AI648684, AI313320, AI627988, AI251221, AI630928, AI340627, AA640779, AI340603, BF904263, BE910373, AV743962, AI587143, AI312146, AI312339, AA572758, AI889168, AI345258, AI348854, AW193000, BE964614, BF817926, BE965432, AW020693, AI457369, AL040243, AI445115, AI620866, AL513699, AW081242, AI610645, AI801325, AI866798, AI932794, AI689248, AI340582, BG110241, AA225339, AA427700, AI270707, BG179993, AV682672, AW827228, AI955467, AI681985, AI684265, BE895585, AW074993, AI349614, AI590415, AI811353, AI354283, BF868928, BE885241, AI564247, BG058398, AI302910, AI955917, AI349256, AW946806, AI312152, AI174394, AV682867, H89138, AW075084, AI567351, AI800433, AI950664, BE048179, AL036288, AI634224, AI349937, AW089572, AI334884, AL039132, AV651436, AI670009, AI349957, AI307708, AI312325, BF981774, AW269097, AI609409, BG036846, AI591420, AW190042, AI572892, AL045266, BF971016, AV682218, AL121286, AI916419, BF925729, BF339322, AI307520, AI925156, AI445237, BE047952, BG180996, AI306613, BE544111, BE885353, AI434256, AV708097, AV712838, BF924882, BF885000, BG113299, AV757028, AA012905, AI917123, AL134999, AW075351, AV682521, AI874166, AL036736, AL036901, BG168696, AW151138, AW268302, BG033723, AW023590, AI306705, AI436456, AI608667, AV682763, W33163, AI282281, BE785868, AW170635, BG250190, AW073994, AL390882.12, AK027164.1, AF056191.1, BC003687.1, AK000432.1, AL512733.1, AK024538.1, AL157482.1, AF177336.1, AL117460.1, X72889.1, AF090934.1, AL359601.1, AK026526.1, BC008488.1, AK024524.1, AK024588.1, BC001045.1, AL136787.1, AB047904.1, AL049452.1, AK025084.1, AK026947.1, AL512750.1, AF090896.1, AL136845.1, AL050146.1, AK026855.1, AK026597.1, AB048954.1, AB056420.1, AL137560.1, AL136749.1, AK027868.1, AK027096.1, AL359583.1, AL136844.1, AB060852.1, AL157431.1, AB060826.1, AB060916.1, AB060825.1, AB055368.1, BC008893.1, AL117435.1, AK027213.1, AK000614.1, AL162083.1, AL049464.1, AK026534.1, AJ242859.1, AL136892.1, AK000137.1, AK025524.1, AL137463.1, AF090943.1, AB048964.1, AK025906.1, BC008070.1, AB047801.1, AB055303.1, AB060887.1, AL359615.1, AK000618.1, AL137550.1, AF225424.1, AL359596.1, AL117583.1, AK026647.1, AL133080.1, AK026629.1, AL133075.1, AF125948.1, AF111847.1, AF146568.1, AL133113.1, BC007199.1, S61953.1, AK026045.1, AB060908.1, AL133557.1, AL136789.1, AB049758.1, AL122093.1, AL133606.1, BC008983.1, BC008382.1, AK026592.1, BC008417.1, AK026353.1, AB055366.1, AL050149.1, AL133016.1, AL442082.1, AL110225.1, BC008365.1, AL117394.1, AB051158.1, AL389982.1, AL117457.1, AK026504.1, AK025092.1, AL122098.1, AL050116.1, AK025772.1, AL080124.1, AL136799.1, BC003683.1, AK026542.1, AK000647.1, AB060863.1, AL110221.1, AL137527.1, AB063070.1, AF218014.1,

					AL049314.1, BC002733.1, AK000083.1, AL137538.1, BC008387.1, AL442072.1, BC006412.1, AL050393.1, AF078844.1, AF091084.1, AL136928.1, X82434.1, AF097996.1, AK025967.1, AK025391.1, AL080159.1, BC008899.1, BC001967.1, AL512754.1, AK026959.1, Z82022.1, AB063046.1, AL137459.1, AB063084.1, AB052200.1, U80742.1, AB056768.1, AB019565.1, AL122123.1, AF230496.1, AL137557.1, AK000445.1, AL136786.1, U42766.1, AL137648.1, AK025491.1, AL050277.1, AL117585.1, AL512689.1, AF219137.1, AF090903.1, AF125949.1, AK026593.1, AF260566.1, AL050108.1, AL133565.1, AL122121.1, AL049466.1, AB055361.1, BC006807.1, AB056421.1, AF090900.1, AK026452.1, AL583915.1, AL512719.1, AB047615.1, AL133640.1, AK026741.1, AK025484.1, AB055315.1, AL050024.1, BC002839.1, AL110196.1, AL122050.1, AJ012755.1, AL110197.1, S78214.1, AK026784.1, AL162006.1, BC007021.1, AL136768.1, AL512765.1, AL136586.1, AF090901.1, AL512718.1, AL080060.1, AB052191.1, AK026086.1, AB048953.1, AL512761.1, AK025339.1, AB063008.1, AK026651.1, AL359618.1, AF183393.1, AL512746.1, AF207829.1, AK026532.1, AL353940.1, AL133560.1, AK000718.1, AL390167.1, U91329.1, AK026865.1, AF106862.1, AF104032.1, AF061943.1, AK000652.1, AL122110.1, AL359941.1, AK027113.1, AB060912.1, Y16645.1, AL049938.1, AL133093.1, AL389978.1, AL512684.1, AK026583.1, AL049430.1, AB050510.1, AL049382.1, AL137271.1, BC004951.1, BC008280.1, AK026744.1, AK025958.1, AK025414.1, AK027204.1, BC008485.1, AB062938.1, AK026630.1, AL136843.1, AK025632.1, AL080127.1, AL162062.1, AK026927.1, AK000323.1, BC004556.1, AL080137.1, AL050138.1, AL137521.1, BC006195.1, AL122049.1, AB055374.1, AL049300.1.
HKBI57	123	876571	1 - 1128	15 - 1142	AL518848, BE795484, BE790580, BE793563, AI005330, AL530857, BE865465, BE740884, BG259765, BE559709, AW972157, BE793925, BF732476, AI523173, AI133648, BF132480, AA741065, BE266365, AW246779, AA483640, AI553793, AA889963, AW731821, AW376863, AI457636, AU159951, AI076501, BE865290, AW250974, BF683810, AI245539, AI160351, AA122216, N70566, AI123318, W04730, AI298575, AI094218, BF840014, AI298397, AA627412, AW474453, BF063304, AI304872, W80875, BE645309, AI829879, AA877594, AW514292, AA721451, AI032434, AA564388, AA723454, AW571641, AW591598, AW605095, AA404537, BF326544, H07869, F13805, AI055951, AA122217, AV693323, AA308813, AI474982, T08020, AI678622, AA284386, AW839757, AW189626, AL530858, BE393850, W80766, BE143803, AA706470, AA319710, AA480437, BE936534, BE166705, AW051083, AA121863, AI432644, AI927233, AI687607, AI924051, AI431307, AI623302, AI431316, AI431238, AI539800, BE897632, AI590043, AI289791, BE883591, BG167830, AI285417, AI866786, AI687588, AI537677, AI494201, AI872315, AI500659, AI866465, AI815232, AI801325, AI500523, AI538850, AI887775, AI582932, AI923989, AI284517, AI872423, AI440260, AI500706, AI445237, AI491776, AW151138, AI889189, AI521560, AI500662, AW151974, AI567971, AI804505, AI815239, AW172723, AI284509, AI582912, AI538885, AI440263, AI889168, AI866573, AI633493, AI434256, AI866469, AI434242, AI805769, AI866691, AI888661, AI500714, AI284513, AI888118, AI285439, AI859991, AI436429, AI355779, AI623736, AI889147, AI581033, AI371228, AW194509, AI491710, AI440252,

					<p>AI926593, AI440238, AI860003, AI610557, AI242736, AW058275, AI828574, AI887499, AI539781, AI539707, AI702065, AI885949, AI285419, AW089557, AI559957, AI521571, AI469775, AI866581, AI866503, AW151132, AI539260, AI567953, AI815150, AI446495, AI431321, AI867068, AI932620, AI890907, AW074057, AI042729, AI889191, AI952433, AI225248, BE885490, AI358271, AI798359, AI282249, AI698352, BF812963, AI371229, BG252929, AI539771, BF811804, AI561170, AL042595, AW151979, AI284516, AI432666, AI289101, AW858522, BF814072, BF811802, AL039508, AW151136, AI866458, BG029667, AI371251, AI493559, AI866510, BG249858, BE826157, BG113493, AI866461, AI923046, BG110517, AI687944, BG176609, AL047611, AI955221, BG257535, AI889157, AL039390, BF795712, AI559976, AI690946, AI567947, AI436438, BG253986, AI648567, AL042787, AL134524, AI433157, AI362495, AI371243, BF796402, AI288076, AL515375, AL042853, AI469764, AV736134, AI432653, AI431323, BE886728, AL042655, AV736402, BF815930, AK023992.1, AK027449.1, BC001215.1, AF152097.1, AL355392.7, AL136763.1, AL133049.1, AL133053.1, AL136825.1, AL133607.1, AL133076.1, AL122101.1, AL049423.1, AL133084.1, AL133070.1, AL133655.1, AL136765.1, AL136781.1, AL110223.1, AB048910.1, AK026784.1, AL133074.1, BC008781.1, BC007294.1, AL133015.1, AL133608.1, AL136828.1, AK026927.1, AF002985.1, AL162008.1, AL117445.1, BC008983.1, AL157482.1, AL122049.1, BC004991.1, AF082324.1, AL133051.1, AB049849.1, AL136808.1, AF057300.1, AF057299.1, AB047623.1, AK026480.1, AK025860.1, AL049557.19, BC003108.1, AL512733.1, AK025484.1, AL512765.1, AC004213.1, AC006039.2, AK000225.1, BC000649.1, BC004314.1, AB047941.1, AL049300.1, BC000253.1, BC004530.1, AL080139.1, AK026912.1, AL389947.1, AL354864.16, AB047953.1, AL162062.1, AL137485.1, AL137254.1, AL353092.6, BC000009.1, AK000486.1, AC008755. 6.</p>
HKGDL36	125	877489	1 - 1038	15 - 1052	<p>BF966686, BF969262, BE798423, BE383172, BG108317, BF438085, BF967072, BF724971, BF310167, BF437374, BF525713, BF725537, BE312863, BE327726, BF526596, BF983368, BF966496, BE392518, BE045542, AI261620, AI628667, AI955247, AI796185, AW024651, BF724972, AI365220, AI767645, BE551437, AW051507, AI199503, AI418919, BF724666, AI039610, AW162506, AI955309, BE673721, AW138191, AI969138, AW583447, AI373491, AI696987, AW583390, AI952012, AW341037, BF310234, AI758216, BF438130, AW013963, AI955147, BE669440, AI768473, D61105, BF592013, AI355910, AI969092, AI913491, AW027769, AI423438, AI968975, AI479582, AW090177, H41372, AI927970, AW300071, AI400855, AI348277, AW771649, AI672352, AI991536, AI421291, BF739771, AW103643, AA894790, BF197412, BF724667, BF197448, AW583609, AW000953, AW299323, AI498193, AA199635, D59847, AV748923, AI560270, AI625846, AI493832, AW590037, AW955700, AI702136, AA877175, AW583672, AA757536, D59877, AA706516, AW393735, D60795, D80419, AI302316, AI248555, D80214, D80684, AI927667, AI627691, AA989221, BE464388, D59878, BE218723, BF346124, AI985164, AW000934, BF967708, AW001692, AI701771, D59848, D59725, AA873392, AA364835, BF431598, H92678, AW135417, AI589246, AW072965, AW163721, AI916619, BF752892, BE964512, AL515163, AW022102, AI783861, AL513839, AA600801, BE621073, BE544111, BF815196, BF910849, BE963809, BF814409, BE784387, BF840099, BE963918, BG170109,</p>

					<p> BE613727, BE880341, BF814360, AW005029, BF921092, AV712606, AV681927, BE967251, BE964621, A1866741, AW059713, BG108334, BE536377, BF929585, A1254754, BF764538, AA824513, AW083804, A1539462, BF129016, A1446605, AL513741, AA830821, BE966699, A1924035, A1445976, BE875966, A1242248, BE885353, BE538466, A1620093, A1537643, A1358042, BE880697, A1683255, A1591412, A1591081, W81248, A1536910, BE964962, AW834325, A1864827, BE048026, A1872159, BE061389, BE964767, A1591057, AW073868, A1863256, A1690449, BE907440, A1884574, F35927, BE878032, BE965121, N95566, AV743128, AV706465, A1445588, BE899377, A1934000, A1280670, A1583578, A1627714, A1500039, AV708075, BE900603, BF752858, AW265004, A1623682, BF341610, AW079032, A1925736, A1252077, A1590787, AW025533, A1267185, BG105895, BE964600, AL513789, F26535, AL048377, BE965527, BE967255, BE964799, AW946864, AL514167, A1627880, BE621140, AV710267, A1678302, A1926878, BE878028, A1633300, BF817402, BF753053, BE875407, BF752999, A1689614, A1624668, BE966390, A1811192, A1866002, F28295, BG260275, BE963286, BF753056, BC002851.1, AF181562.1, AF196971.1, A1012582.1, BC003104.1, BC007248.1, BC001470.1, AF230402.1, BC002948.1, AF352728.1, U77594.1, AK000212.1, AB063077.1, BC003687.1, BC004314.1, AK026865.1, AK025491.1, BC001294.1, AB060908.1, AK025906.1, AL137557.1, AL136752.1, AK000598.1, AL121656.2, BC002816.1, BC002356.1, A1010277.1, BC002397.1, BC004529.1, AL157464.1, BC000785.1, BC000725.1, X95876.1, AB060832.1, BC004324.1, AL080162.1, BC002777.1, AF022813.1, AK027113.1, BC004370.1, AB055374.1, AL137556.1, AK024601.1, AK026164.1, AL512705.1, AK026613.1, BC008417.1, AL512746.1, AL136780.1, AL136864.1, BC001969.1, BC004310.1, BC000235.1, AF028823.2, AF112208.1, AL136767.1, BC003602.1, BC005890.1, AL137665.1, BC004417.1, AL137547.1, AF218034.1, AB049629.1, AF239683.1, AL136799.1, BC008196.1, BC006251.1, AK026590.1, AL049347.1, AK026603.1, AL389978.1, AL049460.1, S7771.1, AL512719.1, BC004937.1, BC005678.1, BC001093.1, AF225424.1, AB063071.1, AB060214.1, AB047904.1, BC002557.1, Y16645.1, AB060893.1, BC001349.1, AL137459.1, BC004195.1, AL512718.1, BC001963.1, AF111847.1, AB060914.1, AL353935.1, AL136766.1, AK026600.1, BC002491.1, BC000778.1, AL096720.1, AL359622.1, AL049314.1, AB047941.1, AK025119.1, BC004333.1, AF205861.1, AL133568.1, AL136586.1, M92439.1, AL136790.1, AL117648.1, AL137657.1, AF069506.1, BC007207.1, AL133081.1, BC004202.1, BC005931.1, AB060839.1, AL080137.1, AB056768.1, M79462.1, AK025410.1, AL390167.1, AK026533.1, AF090934.1, BC003052.1, BC005151.1, BC000217.1, BC008488.1, AL162062.1, BC004131.1, AL136842.1, BC009294.1, AB019565.1, BC000348.1, AK024594.1, AF188698.1, AL122050.1, BC004530.1, AF132676.1, AB056427.1, BC006440.1, AF061836.1, BC000772.1, BC006458.1, AF217991.1, BC003410.1, AL389935.1, BC006133.1, AF348209.1, AL353625.5, BC002911.1, X66975.1, AK024570.1, AK000450.1, BC008070.1, AK024533.1, AB048888.1, AK000432.1, AL133645.1, BC004899.1, AL359596.1, BC002535.1, AK026741.1, BC004383.1, AF271781.1, AL117585.1, AB044547.1, AB063079.1, AK000310.1, AF036268.1, AB049758.1, AL080074.1, AL442082.1, U42766.1, BC004926.1, BC004960.1, BC005872.1, </p>
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HKISB57	126	625956	1 - 1478	15 - 1492	<p>AL049339.1, AF358829.1, AK026086.1, BC003650.1, AB047897.1, BC002798.1, BC007674.1, AB055366.1, AB060929.1, AK025239.1, BC005854.1, BC002342.1, AL359623.1, AL110225.1, AL122118.1, AF321617.1, AC025226.4, AK026649.1, AF271350.1, AK026045.1, AK000652.1, AK000445.1, AL133062.1, BC002519.1, BC004297.1, BC006106.1, BC000094.1, AL136828.1, AL137648.1, BC006196.1, BC002343.1, BC006494.1, BC000316.1, AB060226.1, AL157483.1, AK027142.1, AK000323.1, AK025517.1, BC008025.1, AL353956.1, BC002476.1, AL050092.1, AL096751.1, U91329.1, AF081197.1, AF081195.1, AK025383.1, BC005002.1, AC006357.5, AL080060.1, BC001762.1, BC000386.1, BC005858.1, AB049849.1, BC002539.1, AL162008.1, AK024538.1, BC005007.1, BC002647.1, AB047887.1, AB047623.1, AB060873.1, BC004265.1, AK027081.1, BC001293.1, BC008485.1, BC001045.1, AK027164.1, AL136644.1, AL122098.1, AK000655.1, AK000421.1, S69510.1, AL137284.1.</p> <p>BG253059, AI888563, AW083174, AI890983, BE77527, AI742994, AA581853, BE208188, AA496043, AI749573, AI433172, AA912116, AU152415, AU151244, AA526295, W72233, AI708515, AA029171, AI289783, AA147482, AW001857, BE744941, BF851250, W76470, AI148076, AI619715, W32695, AI973179, BF856405, AA086231, AI536682, AI244167, AW205328, AA112137, AI015550, AI159953, AA449234, AA449289, AI886087, R48602, AW974749, R48705, N57904, W73612, AA515533, AI095398, AA086322, AA554446, AA317019, BE019888, R07096, AA894669, AA112027, T96414, AA923651, T96497, AI581984, AI093238, AW084446, BE834394, T65129, AA100811, BF767404, AA652428, W32694, AW364698, BF371383, AW390788, AI903419, AI903380, AI903350, AA300051, AW886927, H55267, AA029067, AA588851, AA588463, BF931116, BE646329, AW514396, T65909, AW578218, AW800794, R07042, AA625855, AA663955, AA687595, AI581808, R76016, W22074, AA043407, AA436950, H39017, BF814527, AI824576, AI702073, AI698391, AW080090, AI633062, AI608936, BE786043, AI358213, AI306705, AW983832, BE963838, BG179993, AW051258, AI677796, AW051088, BF856017, AI932794, AI366900, AI352497, AI889189, AW983829, AI270183, AW163834, AL514731, AI434468, AI812015, AI249877, AI679672, AW118518, BF812960, AI284131, AW029611, AI468872, AI699011, AI927755, BF792961, BE966388, AI886753, AW827289, AI564719, AV743962, BG108406, AI567846, AV741327, AI573060, AI783504, BG112718, AI620284, AI866770, AW198075, BF032768, AW083778, AL514899, AI611738, AI280732, AI619502, AI680162, AI802542, AW081255, AI280607, AI499285, AI570807, AW004886, AI452560, AW026882, AW151136, AI923370, AI627988, BF812938, AL118781, BF970652, BE789764, AW104724, AI670009, AI863382, AI433157, BE543089, BF812961, AI452993, AI624548, AI659795, AW079572, AI860783, AI633125, BF812426, F27788, AW089179, AI673785, AI915291, AI354998, AW152182, AI537024, AI917252, BE967261, BF725599, AW080746, AL120853, AW129659, AW163554, AI537677, AI499890, AI612852, BF526020, AI174394, AW192461, AI613270, AW105620, AL119863, AI520809, AI923989, AL036673, AI571909, AI803778, AI653979, BG036846, AW192687, AV682249, AL514357, AW839006, AI274507, AI632408, AI288305, AI635067, BG180273, AI612913, AL119828, AV682212, AI590686, AI435268, AI432030, BE048071, AI500588, AI628217, BE047606, AI637748, AW238688, BG029829, AF064238.3,</p>
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HKMMW7	127	581399	1 - 1780	15 - 1794	<p>AJ010306.2, Y13492.2, Z49989.1, AF115564.1, AF115570.1, AF115567.1, AF115569.1, AF115568.1, AL122098.1, AL137533.1, AB056420.1, BC006195.1, BC005858.1, AK024524.1, AL133067.1, AK025092.1, BC001045.1, AL137550.1, AL080159.1, AK026462.1, AK024538.1, AL512733.1, AL050277.1, AL389939.1, S61953.1, AB056421.1, BC008893.1, AL137294.1, BC001963.1, AL389982.1, AF026816.2, AL136844.1, AB060852.1, BC008488.1, Y14314.1, AF260566.1, AL136805.1, AL049283.1, AL512684.1, AK025209.1, AK026593.1, X82434.1, AK026542.1, X72889.1, AL137560.1, AL137271.1, BC004951.1, AB060916.1, AK026532.1, AF183393.1, AL137478.1, AL137556.1, AL583915.1, AK025484.1, AF057300.1, AF057299.1, AK000652.1, AF348209.1, AL353625.5, AK026480.1, AF218014.1, AF225424.1, Z82022.1, AK027213.1, AK027164.1, AK027160.1, AF056191.1, BC003122.1, AF111112.1, AB048974.1, AB062938.1, AL050393.1, AK026534.1, AL122049.1, AL136915.1, AB055361.1, AK025632.1, AL122100.1, BC006525.1, AL110225.1, AL133568.1, BC004556.1, AL136892.1, BC008365.1, BC005678.1, AL080124.1, AK026408.1, AL162002.1, AL122110.1, AK026533.1, U39656.1, AL136893.1, AL050149.1, AK000418.1, AJ299431.1, AB047904.1, AL122093.1, AL050138.1, AL133560.1, AL137463.1, AL136749.1, BC006807.1, AL133557.1, AF262032.1, AB049758.1, AK000323.1, AF146568.1, AF162270.1, AL133113.1, AK025465.1, AL133072.1, AF091084.1, AK026583.1, AK026642.1, AL133640.1, AL359583.1, AK026744.1, AK025084.1, L30117.1, AK000083.1, AL133016.1, AK025708.1, AL353940.1, AL442082.1, U80742.1, AK000718.1, AL110280.1, AK026865.1, AL512750.1, AL162083.1, AF090934.1, AB048919.1, AL359620.1, AL050172.1, AL359618.1, BC004958.1, BC003682.1, AB046642.1, AL110221.1, BC006164.1, BC003684.1, AL512765.1, AL122121.1, AL137292.1, AF271350.1, AL137476.1, AK000391.1, BC008417.1, U58996.2, AB063084.1, AB056809.1, AF090900.1, AF242525.1, AL353956.1, AK026551.1, AL080148.1, AL117435.1, BC009033.1, AK024588.1, AL137557.1, AK026528.1, AK000432.1, BC006440.1, AK026947.1, AK027204.1, AB047801.1, AL117457.1, AL050116.1, AL136586.1, AL137480.1, AJ006417.1, AF061573.2, BC009341.1, AJ012755.1, AL512718.1, BC008070.1, AK027096.1, BC008899.1, AB056427.1, AF217987.1, AB048954.1, BC006494.1, AK026762.1, AK027182.1, AL512689.1, BC002733.1, AK027116.1, AL133075.1, AL133093.1, U78525.1, AL136787.1, BC008387.1, AF106862.1, AL080060.1, AL359941.1, AK000445.1, AB060826.1, BC005890.1, AB048953.1, AB050410.1, AB050510.1, AK026629.1, AK026045.1, AB050534.1, AF177336.1, AK025414.1, AL117460.1, AL136768.1, AF090903.1, AB052200.1, AK026927.1, AL117440.1, AY033593.1, AL133565.1, AL390167.1, L19437.2, AK026592.1, AK024601.1, AB063008.1, AB055374.1, AK025958.1, AJ242859.1, AF113222.1, BC009212.1, AK026452.1, AK025254.1, AB060214.1, AL110222.1, X53587.1, AK026959.1, AL162008.1, AF218031.1, BC005151.1, AB047615.1, BC004370.1, BC006103.1, AY034001.1, AK000486.1, AL133098.1, BC003548.1, AL050108.1, AL122118.1, AB062978.1, AL136789.1, AL049452.1, AK025391.1, BC008284.1, AK000647.1, AL136786.1.</p> <p>AI524360, AA582463, AW970030, AW088049, BF845261, AV744082, BG166773, BF970654,</p>
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4					<p>AL137859.3, AC008784.6, AC022382.3, AC079844.3, AB038490.1, AC007917.15, AL158070.11, AL136231.12, AP000555.1, Z96074.4, AC006430.22, AP001695.1, AL354811.13, AC078958.30, D87675.1, AL138849.12, AC004019.20, AL391415.12, AC079950.23, AL117694.5, AC004935.1, AL121834.20, AL109921.21, AC008551.5, AF200465.1, AC008892.5, AC068799.14, AC006036.3, AC005725.1, AC015982.9, AL391262.3, AC004104.1, AC005079.6, AL132988.4, AP000692.1, AL590116.8, AL158144.15, AC005305.1, AC003049.1, AL022313.1, AC005520.2, AL353135.32, AL117377.18, AC025887.4, AC004468.1, AC083876.2, AC004774.1, AC004634.1, AL121900.26, AC034198.6, AC006460.3, AC005522.2, AC018828.3, AC067742.5, AC022383.3, AL161655.8, AL445686.14, AL031224.1, AP000128.1, AP000206.1, AL021154.1, AC009006.6, AF111167.2, AL589782.7, AL590785.7, AC021016.4, AL133387.8, AC006115.1, AC026439.3, AL034394.2.</p>
HLDON23	129	636083	1 - 1248	15 - 1262	<p>AL529086, BE904120, BF337766, BF345489, AV706125, AL681123, BF002270, BF055322, BE856092, BE305227, BE219427, BF438375, BG149525, BF057786, BF590112, BF196165, AL741848, AL636347, AI973055, AI554720, AI871117, BE220195, AI745311, AW192924, AW340966, AA706712, AI091179, BF445900, BE645773, AI677802, AI889659, AI804323, AI688189, AW673266, AI298377, BE046787, AA535027, AW612722, AI830304, AW675294, AI139157, AW089901, AA410579, AW073842, AW316637, AA417232, AA416567, AI827376, AI372513, AA411560, AW001905, AI796719, AW673062, AI334363, AI085075, AI400032, AI452964, AA308319, AI888902, AI400560, T33187, AA877699, AI332395, AI372512, AA485507, AA017127, BG178589, R85136, AV705959, AL526358, BG056798, H94860, BF476221, AW016699, BF594282, R18537, AA988884, AI925753, AA993373, AW953175, W05059, AI263531, AA282629, F29641, R01402, AA625328, AA126985, AA354334, H58095, BE251679, AW662030, AI559961, AW337874, AA282410, AI014243, AI671403, R41526, AA485352, R43109, Z39066, BF925559, F04091, R01401, W04796, AV751453, BE871534, AA128150, AW375092, BF237662, BE155754, T25085, F17839, AW371533, N74669, AW058382, AW371557, BF063353, AL360256.1, AL117482.1.</p>
HLDQR62	130	753742	1 - 2558	15 - 2572	<p>BE876197, AU133975, AW170131, AV723948, BG178057, AV652458, AW836234, AW608052, AA047046, BF104746, AA486037, BE395776, AW385580, AA488655, BE699041, AA932253, BG104619, BF671350, AA854943, AA418105, AA829456, AA243385, BE699051, BE936060, AI346694, AA418007, AA503398, AA053835, AW067836, AA878478, AI309218, BF820483, AA287990, W37960, AI401102, AI279485, W37900, AI423510, AA610711, AI050735, BF939011, BE699047, AA701403, W30974, AA017371, AW385388, AA911160, BF928600, HI0281, W32542, AA133579, AV721259, H81907, BE908122, HI1712, AA657490, H09562, R97956, BF810354, N68428, BF841567, AA018681, BF810349, AW838671, AW274397, BE699044, BF737894, HI17436, AA133578, T03483, BF529092, BE699011, R93915, T84200, HI0225, R97955, N91220, F09018, BE244933, BE697384, AW474873, Z43397, AA677745, F11358, AW838680, Z42508, H08994, HI1779, R18755, AW067888, H86384, R20010, R44826, T78746, BE546845, BF768165, AA676360, Z41104, R12303, R61069, H80952, H01770, BF362799, AA857228, BE092626, AW361033, BE246721, R12953, F11514,</p>

					AA298600, AA233314, H82000, Z45386, AA047038, AA988879, AA776420, R61792, BF925722, F02025, H37922, AA946813, AA058662, BE793798, AA298811, AW954042, AI024907, AA515707, AA579408, C02381, H38137, H80857, AA190438, AA059270, AW953912, W32541, AI253018, BF755527, AA252608, H39230, BF087406, BF841077, BE699066, F09175, AW608049, R36072, AW607934, AW242636, F02790, AA018740, BE092426, N47523, AW951415, BE872758, AA670010, BF793691, H86054, BE699208, AA017201, AA059226, BE857637, BG011131, AA233315, AW169463, BE935974, AA910836, BF756516, AA504287, AA489248, AW452612, BE858890, BE699076, AA953019, AA191764, BF930488, BE746764, AA552521, BF932022, BE080981, AW385586, BE092405, BE047109, AW838675, BE074538, AB046801.1, AC026749.5, AC026437.5, AC010491.3, AK001799.1, AF274753. 1.
HLDQU79	131	740755	1 - 1474	15 - 1488	BG256275, BE867624, BE907396, BE855521, BF034422, BF530803, AW959247, BE782005, AI126689, AL121446, AA757065, AW630129, BF768037, BE746763, AA206154, AA460401, AI276320, BF998689, AA295243, BE242732, BG035901, AL040350, BE242810, T86168, BF983867, W05088, AA347337, BG252443, AI133502, AF064093. 1.
HLHAL68	132	684216	1 - 690	15 - 704	AA359084, AC018797.4, AF224669.1, AF283321.1, AC007883.3, AC006038.2, AC034251.5, AC006345.4, AC008149.14, AL355392.7, AC006057.5, AC084864.2, AL354720.14, AC084865.2, AC006435. 7.
HLIBD68	133	778073	1 - 1008	15 - 1022	AL538046, BF975484, BG260893, BF062040, AW250850, AW954319, BG118275, AI633756, AI436560, BE646174, AA975057, AW302253, AI651397, AI825665, AI479926, AI635567, AI612806, AI640598, AI653427, AI248825, BF770160, AI333221, AA609320, AI916748, BF346659, AW001438, BF941021, AA397893, AI083783, AA399663, AA302889, AA484860, AI659648, BF222019, AI692578, R49550, AW016187, AA393712, AI673346, D80738, D81106, D81495, D81643, C15479, AI696498, C15522, R42643, AI761655, AA302888, D81794, D81487, D60344, AA302884, AA302883, BF813253, AA091824, BE743563, N49704, AI476597, D81533, N87760, BE396027, AA352126, AA281538, AA280240, AL133447. 1.
HLICQ90	134	791828	1 - 1752	15 - 1766	BF980403, BF726329, AI984197, AI192533, AI559494, AI378638, AA430026, AI061413, AW172705, BG165333, AI190915, AA430235, N62729, AI689890, AI360764, AA705532, H90333, H30177, T99745, H78217, T86019, H26993, T91236, AV645894, AA330598, N75483, H42449, BE766728, AW135351, AA976652, AA383620, BE220880, AI630095, BF381551, BF767606, BE087130, H42847, W05293, AA911697, AI659925, BE766726, H82733, T99746, BF889067, AW955970, AW971740, AI432644, AI431328, AI623302, AW968355, AI431347, AW972091, BE672759, AI432653, AI431230, AI432654, AI432655, AI431310, AI431312, AW081103, AI432677, AW968356, AI431323, AW972093, AW968729, AI431354, AI432661, BE672719, AI431307, AI431316, BE672732, AI431337, AI432650, BE672745, BE672748, AI431238, AI492519, AI432675, AI431350, AI431231, BE672767, AW972092, AI432651, AI432647, AI431243, AI431330, BF448552, BE672742, AI432662, AI431248, BE672644, AI432657, BE672774, AI432649, AW972090, AI791349, AI431257, AI432665, AI431247, AI431318, BE672738, BE672792, AI431235, AI431321, AI431315, AI431246, AI432643, BE672743, AL042519,

HLQDR48	135	1307726	1 - 975	15 - 989	BE672640, AW129223, AL042931, BE672622, BE672627, AI492510, AL042729, AL042832, AL047611, BE672754, BE672626, AL043295, AL357075.17, AF064854.1, AL133082. 1. AV655891, AV718605, AV690404, AV719284, AA923549, AI950351, AV656411, AV720179, AV654765, AV656119, AV697855, BF511595, AC011472.7, AF271350. 1.
HLTHR66	136	699812	1 - 2272	15 - 2286	AW978874, BF507862, BF033134, AL135232, AI673052, AW612437, AW880652, BF508030, AW118937, AI912990, AI651420, AI754531, AI285856, BF431306, AI760176, AI805972, BF511821, AI123209, AW001864, AI377932, AI141443, AI743946, HI9020, BE857717, AW962968, AI221575, AA588506, BF475287, AA026012, AI249502, AI660528, AI949710, R68887, AV653095, AA026000, R77684, HI9313, AI460280, AA829761, AA357748, BF511571, R77685, BE671786, AA084602, AI687732, AW889295, BE002919, AI812062, BF365444, C21025, AI136231.12, AF147395. 1.
HLTIP94	137	1087335	1 - 1226	15 - 1240	AA552985, AA314716, BE778519, BE894256, BE779796, AA228139, AI802948, AC005325. 1.
HLWAA17	138	629552	1 - 983	15 - 997	AL522002, BF305304, AL521608, BE732838, BE899550, BF344719, BG115015, BG109203, BF982386, BE410162, BE735023, BE901175, BG117962, BE281306, BG165427, BF793440, BE901577, BE872442, BF316646, BE409982, BF982251, BF970528, BE262711, BE299415, BF340859, BE386152, BF569778, BE281612, BF305644, BG251248, BF673757, BF183244, BE547252, AL521166, BF237978, BG249255, BE280374, BE301893, BG109330, BG164142, AL522550, BE018945, BG170896, AW732476, BE779176, BE018944, AL532064, AW250139, AA580387, H20615, BE741195, BE736037, BE727171, AI752100, BE870251, BE742694, BE883834, Z42865, W21970, AA873793, AW579408, BF753347, AA204913, AA206511, AA158660, BF971112, H66924, R25678, AA233944, BE743048, BE743976, BF304498, BE546682, BG112068, BF317329, BE278514, BF878947, BE744899, Z25248, BG248593, AW675147, T56764, AA368717, BE793472, AW956985, BE246887, BE298316, BE410692, BE707861, BF125052, BE388318, BF970723, BF675911, BE868990, BF031826, AA380216, AJ271671.1, BC007886.1, BC002563.1, AJ243649.1, BC003152.1, AF151829.1, AF132942.1, AJ243650.1, AC004832.3, AC005585. 1.
HLWBK05	139	765310	1 - 2369	15 - 2383	AL536493, AL514199, AL157671, BG260370, BE379053, BG252836, AL529147, AL515380, AL514200, BG104666, BG114729, AL529146, BF967759, BF527200, BF316407, BG261268, BF184232, BF115962, AW965314, AW005623, AW973905, BG171109, BE736594, BF529773, AI928466, AW516590, BF966979, BE046448, AW014546, BE876855, BG254307, AW958252, W87297, BF526617, AW959008, AA164613, BF439848, AW000936, AI703274, N24392, AI580919, AA037159, AI686912, AA179191, AW594515, AW085214, BE671804, AI168495, BE296663, AA868707, AA225014, AA888872, AI219983, AA179201, AI660755, AA164612, AI334991, AA420527, H97664, AW510978, AA988373, R70657, AA576605, AA437178, AA628293, H10567, N36611, BF966853, AA970653, AI806255, AA224953, BE296638, W39077, AW242291, AA594662, H99143, AW078769, AI679580, AI269095, N94194, AI680017, AA844022, H23755, BF966096, AA602349, BE164717, N99359, BE328493, W87353, R46707, AA889625, AA573514, R77834, BE090735, N25981, R51410, BF247470, R25551, AA398028, H80504, H48364, AA470783, AW207718, H06507, R64682, BE904435, AA426463, R12724, H06563, R64681, N63835, BF377563, R39776, R16671, BF966194, AA332170,

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HLWBY76	140	797609	1 - 2067	15 - 2081	AA923172, AI139607, AI269739, AI802946, N30680, AI277957, AI277237, BE715040, BE838082, BF354274, AW797336, AW797335, BF987948, AW873630, AI806044, AK026806.1, AC003991.1, AK027807. 1.
HLWCF05	141	460619	1 - 632	15 - 646	AW673972, AA524980, AI961840, AW515257, AA877458, AI336752, AW070880, N66443, AA528268, AI273991, N26777, AA004802, BF990906, AA700372, AI290414, AA906772, AI243008, HI17960, AA502507, AA860313, AW470183, H84037, BF348530, R54094, BF764578, H84462, R30859, BF764695, AI864306, AW022917, AW970612, D45536, AI908718, BF878700, AW999226, BC003414.1, AL450487.17, AK025020. 1.
HLIYAC95	142	778075	1 - 298	15 - 312	AV764526.
HLIYAP91	144	553514	1 - 1262	15 - 1276	AA464480, AI738416, AW970172, BF346852, BE004609, AI097351, AI051171, AW085704, N50904, AI950137, AI718945, H64092, BG236491, AI964070, AA514204, AW401489, W76242, H64144, AW204133, AA295625, AW388106, BF751672, AA693868.
HLIYES38	145	638042	1 - 1209	15 - 1223	AV701925, BE883545, BE250577, BE736918, BE616582, BF793477, AV706319, BF338817, BF346135, BE728115, BE615376, BG250960, BG032917, AU139668, BF951636, BF811794, BE899007, BE898175, BF217767, AL133895, AA225638, AU121535, BE531051, AU135520, AW899342, AA601152, BF675027, AA601227, BE154390, BF911201, BE385152, BF680445, BE264980, BE386373, AA715194, BF874267, BF871285, AA826146, AW023095, AW957880, AW957801, AW962273, AV732690, AA307661, BF882363, AW845664, AV749263, BF197329, AA779025, AA489803, AW872342, BF815608, AV748578, BF957961, AI380547, AA833581, AA243106, AW939910, BE304382, BF877837, BE141836, AV750972, AW962826, BF982391, AW938878, AU116940, BF203663, AA503299, AV652861, H02956, T57668, T47541, BF763870, AW865469, AV731015, BF207674, AI940701, BE184422, AA280232, BE792178, BF829537, BF767788, BF957954, AV683302, AV698434, AA258511, AI918674, AA121877, T07838, AA804919, AW515786, AA281292, AW865403, AU140348, BF238662, AA353112, BF732306, BF940980, T84195, AA431655, T06482, AI440300, H67786, AV715734, BE565499, AA630813, BF673583, AI761174, BF812273, AA593381, N62150, AA487808, W22010, AW898213, AW963317, AV653743, H67930, AI940708, AW864780, AA359714, AI052560, T07383, AW899527, AW999271, AW845678, AA649067, AW898920, AA356190, T97032, AA434462, AA221018, R01106, AA418919, AA431294, BF873657, AW630075, H73439, AA583363, T81895, T47477, BE177666, BE083070, BF951580, AW845665, AV729748, AA720812, AA577789,

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						AC016617.5, AC004845.2, AC012152.12, AL445669.9, AL163248.2, AF207955.1, AC004668.1, AF109076.1, AC013562.6, AL139231. 13.
HMADK33	146	561941	1 - 850	15 - 864		AL538273, AW139111, AA663592, AI582741, AL120259, H51572, AI122619, AI124509, BF366373, R86660, H50906, R86835, BF836623, BE884648, AF070673.1, AF030196.1, AL161976.1, BC005837. 1.
HMADS41	147	596831	1 - 1253	15 - 1267		BE740695, BE739906, BE899124, BE742745, BF685920, BF971897, BF684948, BE336652, BE747520, BE925550, AI733012, AI492192, BE207602, AW275042, AA954656, AW139807, AI791409, AW136444, AI361524, BE207644, AI762361, AI762373, AI246377, BF684146, AA306161, BF062047, BF222947, AW003832, BG028044, AA865078, AA402599, N32269, BC007725.1, AF123757.1, AF123758.1, AF123759.1, AF123760.1, AF123761. 1.
HMAMII5	148	1352406	1 - 1244	15 - 1258		BE790239, AI114496, BE047613, AI609021, AI478544, AI949665, R96283, AI205799, W39248, AI670908, T70976, AA070919, AI243978, AW854183, AI796472, BF883407, AW975683, AA654405, AI125888, AA730911, AA545731, BE222003, AA730927, C21177, AA721678, AI478489, AL137139.9, AL139035. 27.
HMCIFY13	149	635301	1 - 869	15 - 883		BF026299, BE277091, AI343297, BF027218, BE390121, BE387283, AL514638, BE388858, AI364111, BE389119, AI668959, BE391988, AW206551, AA676232, BE870993, BF002101, BE277034, BE729557, BE276352, BF125430, BF896609, BE386944, AW207225, AA551687, BE718320, BF131318, AI990714, BE693868.
HMDAB56	150	560676	1 - 1451	15 - 1465		AI075053, AW972336, AI199257, AA493693, N80663, AW879550, AL138455, AA633753, AA640410, AA640430, AW815064, BF820510, AA018283, AL037554, BG033220, BF822854, AV759329, BG033926, AL120343, BE062169, BF679557, AV757425, AI631355, AW129526, AV710289, BF868399, AW063373, BF437493, AW936354, AI094787, AW500029, BF915002, AA908411, AV760207, AV761925, AW975971, BF666395, BE858219, AV764035, AU137841, BF679274, BG002515, BF698704, BE064275, AA493136, AI700109, BE883107, BF699964, AI918465, AA507547, AI805123, AP002088.2, AC008014.5, AC009470.4, AC011450.4, AL133480.9, AL356244.12, AP000493.1, AC008521.5, AL353741.16, AC004638.1, AL139148.11, AC011475.6, AL158832.13, AC004634.1, AC005102.1, AL135749.3, AC010105.12, AC000088.2, AC019197.7, AL133214.12, AP000901.5, AC008891.7, AC021188.6, AL049776.3, AL117355.5, AC002128.1, AL450483.1, AC007774.1, AL080315.18, AC008622.5, AL135901.23, AP001692.1, Z84485.1, AC007097.4, Z84480.1, AC022415.5, AC008747.5, AC000082.4, AC020908.6, AF121897.2, Z98747.1, AC010422.7, Z84720.1, AL109921.21, AC090944.1, AC074338.1, AC007318.4, AL136219.17, AC004841.2, AC003109.1, U82668.1, AC003103.1, AC020977.5, AF057280.1, L44140.1, AC004774.1, AC011242.8, AC020913.6, AL354935.23, AC069080.12, AL389888.8, AC007036.3, AL136359.13, AC005746.1, AC006441.13, AL133453.3, AC084732.1, AL353194.13, AC004466.1, AC004253.1, AC025165.27, AL160175.5, AC005840.2, AP000251.1, AC007225.2, AL161779.32, AL033378.12, AL359397.3, AL022725.8, AL159977.10, AP001412.2, AF196779.1, AC025765.5, AC007388.3, AC016697.8, AC006023.2,

HMEED18	151	560775	1 - 1355	15 - 1369	AF334404.1, U52111.2, AC008896.5, AL121655.1, AP003117.2, AC009320.7, AC004087.1, AL121992.24, AL136304.10, AL138759.20, AL031228.1, AC006211.1, AL121752.13, AL157406.19, AC025418.23, AC007012.1, AC006548.20, AL354670. 4.
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HMEFT54	152	520307	1 - 582	15 - 596	A1925461, A1187417, AA527170, W51933, AA534506, A1699870, AA430389, AW264729, AA284284, D20078, A1350867, AW131222, W48637, AA400891, A1458334, A1168826, AA400960, BF590627, AV719049, AV699669, A1557751, AW962245, AW975618, AA365173, Z21582, C14298, C14331, C15076, AV699550, AV724520, AW973541, AV718692, AW950117, D80064, AV719758, AV718489, AW949498, D59787, D59467, AA526218, AA701131, F13647, AW817409, AA434346, D80164, AV729929, AW964468, A1201668, D59889, D80195, AA507526, AV720791, AV718530, A1694178, D81030, BF382730, AV720203, AW960553, D50995, AV700889, BE148028, AU119190, R20046, BE001177, AW949645, D80196, BE748599, D51423, T41134, BF837744, AV718800, BF876179, D80212, C14227, BC002933.1, AK026989.1, AF254260.1, AL136917.1, BC008301.1, AF086205.1, AF254860.1, AC090939.1, AC005230.1, AF037338.1, AC004823.1, AC004922.2, AC020716.3, Z95116.1, AC025166.7, AL445184.11, AC009131.6, AC006581.16, AC010530.7, AP000172.1, AC003101.1, AP000057.1, AC005038.5, AP000125.1, BC005232.1, AC002407.1, AL031985.10, AC007308.13, AC002492.1, AC007021.3, AC012476.8, AP000688.1, Z98884.11, AC006241.1, AL355312.24, AL354932.26, AC004526.1, AC007387.3, AF283320.1, AC008543.7,



					AC034193.4, Z83851.17, AC005529.7, AC007193.1, AC018828.3, AC022383.3, AL158159.14, AC018808.4, AP001721.1, AC083873.3, AC004476.1, AL136365.9, AL096791.12, AC008009.4, AC005670.1, AC008524.6, AL031673.19, AL139317.5, AC005531.1, AC008397.7, AF215937.1, AC011811.42, U80017.1, AC006071.1, AL15828.14, AC008969.5, AL590002.7, U53331.1, AL354685.17, AL157877.11, AL442203.12, AL096701.14, AL160269.14, AC006312.8, AL512600.5, AP000030.1, AL445237.16, AC010271.6, AC010326.6, AC006571.12, AL034379.8, AC004685.1, AL023807.6, AC022415.5, AL121747.41, AL161669.5, AC000025.2, AL121886.22, AC018663.3, AC020983.7, AC010183.6, AC073366.3, AL359402.3, AC005015.2, AC005527.3, AC005823.1, AC026464.6, AL138878.10, AC005585.1, AC006480.3, AC010422.7, AC004832.3, AC004973.1, AC005039.1, AC004825. 2.
HMEGF92	153	520304	1 - 615	15 - 629	T65556, BF952979, F09666, AA995112, AA983746, AA983748, AP001972. 4.
HMSDL37	154	973996	1 - 2483	15 - 2497	BF358189, BF358186, BF358188, BF673854, AV762975, AA481760, AL042906, BE908602, AU154050, AU158859, AI310464, AA113159, AV718718, AW080062, AI952885, AL042905, BG029899, AA679794, BF813805, BE206133, AL048969, AI132963, AW401509, AV700988, AA113272, N49425, BF968610, AW975169, AA524604, AW157616, BE300645, AW008089, AV699423, AW976010, AV700654, BF679169, AI016704, N80210, AW151713, AU117926, AA427470, AW957502, AV760701, AI631119, N48230, BE895796, AW962035, AW979158, BF673743, AL534685, AA833875, AA833896, BF926318, BE061906, AA081138, AL044339, AW268329, AW960015, BG254652, AW600804, AU140392, BF820678, BF668559, AV764259, AA572968, BF736198, AV734543, BG22875, AW897556, BF892846, AC022001.3, AC018811.4, AC018494.6, AL353810.9, AC005553.1, AL139396.17, AL020995.14, AL163151.1, AL021918.1, AC022534.7, AL135903.12, AL161443.13, AC007912.6, AC018684.3, AC019052.7, AL163248.2, AJ400877.1, AC006313.1, AC022401.3, AC025165.27, AF274857.1, AL445186.4, AL137782.9, AL139322.13, AL355520.8, AC003065.1, AC004813.2, AE000659.1, AL139109.14, AC027670.4, AC021396.6, AC005033.1, AC007251.3, AC015723.8, AL392106.4, AC004073.1, AC007963.7, AC006544.19, AL353788.33, AL133500.3, AL512641.9, AC010376.5, AC073964.3, AC004650.1, AL157955.5, AL358372.11, AL359077.10, AL137918.4, AL035608.11, AL138783.6, AL135924.11, AP001189.4, AP002453.3, AL133373.5, AL391122.9, AL023876.2, AL163209.2, AC021093.16, AP001719.1, AC068643.27, AL121755.23, AC007068.17, AL359332.2, AL133241.3, AC007611.5, AL357060.31, AC078841.4, AL138880.14, AL159140.4, AL513264.8, AL138920.11, AC004021.1, Z92547.1, AC068102.4, AC089987.26, AC009289.8, AL163280.2, AC010282.5, AL157827.17, AJ006997.1, AC005066.1, AL163303.2, AC009122.8, AL035090.10, AL359205.15, AL133417.10, AC090497.2, AC007097.4, AC005280.3, AL359400.4, AC010591.8, AL354868.10, AP001718.1, AF131216.1, AC068312.4, AL109865.36, Z84480.1, AC009404.5, AC006543.7, AC007510.6, AL160162.11, AL354942.10, AC005862.1, AL136090.12, AC084882.2, AL353812.13, AC022740.4, AC008863.7, AC018797.4, AC006348.3, AL359644.10, AC008701.5, AC087427.2, AC074391.5, AL035407.15,

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HMSFI26	155	560229	1 - 1203	15 - 1217	BF902399, W89152, BE391139, AW975663, A767864, AW020255, AW021440, AI024622, AA730474, AA551532, AC069548.4, AC004906.3, AC004675.1, AC006965.3, AF088219.1, AL121574.19, AL139109.14, AC004813.2, AL162231.20, AC013734.4, AC012459.7, AL157955.5, AL391827.18, AC022407.6, AL034422.24, AC004216.1, AC011551.3, AL355336.15, Z83822.1, AC010252.3, AC008720.6, AL391122.9, AC000353.27, AC012377.5, AC011816.17, AC004408.1, AC007363.3, AC073101.7, AC010092.4, AC016396.5, AL117355.5, AC022201.4, AF235098.1, AL157372.18, AC007228.1, AL445237.16, AC008066.4, AL591770.1, AL162831.5, AP000355.1, AC026770.6, AL353588.25, AC006461.2, AC005840.2, AC005912.1, AC011456.2, AC009137.6, AL035079.14, AB042297.1, AL365400.19, AC003950.1, AC027126.4, Z98884.11, AL034369.1, AL031670.6, AC090955.2, AL157893.16, AC004685.1, AL133500.3, AC011497.6, AC018500.3, AL158206.8, AC019171.4, AC025168.7, AL034346.31, AC005736.1, AL133279.7, AL391724.7, AC002565.1, AP000284.1, AL080315.18, AL133410.31.
HMSJU68	156	427121	1 - 1109	15 - 1123	AV742802, AV736824, AV762141, AV753828, AV762045, BF916188, AV760835, BG222151, BG223218, BF061262, BF941567, AA828594, AW516505, BE676909, AA577958, BF060915, BG222210, AW873282, AW275790, AW276788, BE094185, AA558345, AA654640, AV743295, AA558510, BE676942, AA557706, AA557822, AW207035, BG2223416, AW265566, AA559325,

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HMTBI36	157	1301451	1 - 3374	15 - 3388	<p>BG256587, BE548463, AL134548, BE867461, BE409149, AW854259, AW854064, AI968217, AI651409, BF828833, BG258304, AL134549, BF825872, AI760574, AW502392, BF769439, AI146791, BF828754, AW503066, AI917343, BF846301, AL135082, AW001418, AI964094, AA845693, AW406355, AI203511, AA527307, AA232749, AW014101, AI972765, AI963870, BF892538, AI911155, AW854215, AI573189, AI970351, AI951888, AW854211, BF590826, BF868515, AI432373, AW854189, AI671531, AA741075, AA527993, BF931296, AI147562, AI650589, AA535004, AA809634, AI523816, AI372088, BE504805, AI654213, BG117158, R73344, W16731, AI810884, AI376373, AI867208, AI684987, AI952939, AA504770, AI439038, BF904642, AA927544, AW505179, AI336803, AI631696, AI420438, AI288066, AW501928, BF826497, AW504864, AW013985, BF760209, BF894715, AA829400, AW500832, AA653458, AI582571, AI867525, AI637622, AA483816, AA491154, AA836167, AV650735, AI587126, AI873559, BE219008, AA505113, BE734806, AI651931, AI638281, AI760522, AI400323, BE840233, BE840224, AL134637, AI783674, AI825752, H26511, AA825621, AA926792, BE840052, BF899615, AI742276, BE505014, AW881791, AA505879, AI673191, BF064023, AW087760, BE074795, AI380678, AI341372, AA491313, AI339197, AI971063, AI673213, AI627934, BE825164, AI653411, AA421004, BE763396, N90130, AI366056, W68390, BE763404, AI382284, AW779768, BF955986, AI653256, AW137621, AI921836, AA489461, AA595019, AI867819,</p>

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HMVBS81	158	639203	1 - 515	15 - 529	AW080812, AW082817, AI951822, AW328562, BE138773, AI453744, AW246456, AW248692, AI953814, AA916922, AW166193, BE741575, AI189652, AI554578, BE207752, AW051430, AI143755, AW631158, AI378866, AA602780, AW166148, AI346750, AA402608, AI191618, AA643353, BE207747, AA703840, BF969135, AA503856, AI991172, AI150232, AI885695, BE312018, AA599791, BF940193, AI951334, AI192449, AI423588, AI089026, AI564055, AI160783, BE904552, BE675401, AA722619, AI333580, BE465600, AI147788, AI201929, N39330, AI806345, AA740539, AI359694, BF569026, BG111020, AW078736, W42999, AA915948, BG231541, AI453740, AA845228, AA128902, AI262427, BG111584, AW005011, AI191380, AA838219, N93880, ALS29784, AI289245, AA975577, AA654241, BE270980, R17925, AA455946, AA858122, ALS29713, AW070627, AW068993, AA480313, AW249124, ALS30076, AL044257, AW381690, AW381728, AI073423, AW606063, AW381754, AW381773, W40373, H84216, AW381761, AW381723, AA032144, AW381716, AA639632, BE151932, AI284233, AW606042, AW606073, ALS30075, AW381757, AW381711, BE151941, AW606072, H82810, AW328561, BE151934, AW606039, AI001133, D20808, F35123, AW606054, AW381758, F21453, BE909136, AI866123, T50401, AL526916, AI26629, AA282016, AW881457, AA308337, AA134834, AW364188, BG024191, ALS29714, AI220753, AW601155, AI186566, H48575, BE908027, BE265069, AW469208, BF531105, AW182036, BE733058, AI202946, BE409400, AW250560, BE408657, AA774739, BE514152, AI902442, AA448447, BE792882, BE269512, AW951942, W45258, AW381677, AW885253, BF125578, AW885254, AW996198, H48844, AA402390, AI874330, AA032143, BF806199, BC001299.1, AF004876. 1.
HMWDC2 8	159	460487	1 - 1132	15 - 1146	BF511110, BF511098, BF507863, W52839, AW194969, AI199267, R68505, AI521938, R46033, W81166, BE000169, N47371, BE814496, W81165, AA086195, T64991, AI827849, AI816972, BF592053, AI797732.
HMWFT65	160	562063	1 - 1332	15 - 1346	AW795416, AL121287, AL133445.4, Z85996.1, AL034548.25, Z98304.1, AC004953.1, AC068799.14, AC074121.16, AC004905.1, AL031431.8, AC003982.1, AC006487.8, AC005971.5, AL050335.32, AL009181.1, AC010271.6, AC006483. 3.
HNEEE24	161	553558	1 - 1065	15 - 1079	BE695767, H18634, R44271, AA022988, AA454219, AA454220, AA022950, AA429414, BF112103, AI183463, AW293235, AA584870, AI608821, AA564655, AI467968, H69890, Z95152.1, Z77249.1, AC004837.1, AL050335.32, AC009399.5, AF222686.1, AD000090.1, AC069539.4, AL139080.11, AL117338.15, AC005000.2, AP000427.3, AF039905.1, AC027319.5, AC004996.1,

HNFFC43	162	753337	1 - 2089	15 - 2103	<p>AC010328.4, AP000043.1, AP000111.1, AP001716.1, AP000424.3, AP000292.1, AC073321.4, AL133330.14, AL138743.5, AL050338.12, AL445423.13, AC068715.5, AC009003.7, AL450026.10, AC008493.4, AL355334.26, AC002300.1.</p> <p>AL048903, AI678076, BF527660, BE728354, BF317174, BE409263, AL530934, AL042801, BE729268, AL041340, AL530935, BE314879, AL042802, AW190561, BE1313085, AI961484, AU154235, AU132769, AW027201, AI424792, AL524550, AA864499, AI432437, AA917094, AI934618, BE327057, BE383358, AI499074, AI344032, AI955647, BG253760, AA572961, AL048902, AW769938, BF509684, BE208853, AI342638, AI761488, AW732625, BE259667, AW974120, AI564533, W51904, AW961340, AI289643, AW971194, AW272378, BE297579, AI867205, AI796156, AA884306, BF002574, BF927739, BE885728, BF847648, AA456581, AA918441, AL524551, BF918942, AI766564, AW769937, AA493778, BF918936, AA304712, BF869582, AI168435, AU126961, AA298993, AA377693, AW769673, AI383037, H67555, AA322347, AA221032, AA713594, AI366484, AI039675, BE273248, F24965, AW797208, AA426295, AA322180, AA322590, BF919436, BF919454, BF919453, BF919451, AW178871, AI538564, BF752997, AI766348, AI701097, AW080090, AI367680, BF812961, AI619820, AI633125, AI828682, AI818240, AW152182, BF811804, AI796113, BF968679, BF669151, AI800648, AI500714, AI702073, AI884318, AI590043, AI868680, BG122005, AA740450, AI866469, AI971615, AI345415, AI934259, AI570056, AI433157, AL046466, AI819545, AI499570, AI698391, AI440448, AI915291, AI434731, AI445829, AI889189, AI638644, AI370623, AW188525, AW008226, AI699823, T69241, AI635634, AW148363, AI818350, AW089844, AI686817, AI376425, AI609375, AW051088, AI744268, AV736995, BF970652, AI569637, AW163834, AI270295, BE393784, AI471282, AW075381, AL043355, AI872423, AI801460, AI620864, W74529, AI421252, BF812938, AW081256, AI581362, AL513817, AW193911, AI670009, AI871697, AI537261, AI950729, AV709679, AI651840, AI281757, AI619502, AI591387, AW168822, AI473536, AW196720, AI345612, AI620056, AW834282, AL046595, AI677796, AI582932, N21402, AI922266, AI500061, AI474646, AI345416, AW079409, AA641818, AI621341, AI702068, AW081383, AI633198, BF814761, AI619662, T49776, AI565172, AI696714, AV747571, AI524179, BF766531, AI366900, AI521560, BF925771, AI927233, AI536638, AI479292, AI564719, AW027898, AI419826, AI432969, AI432030, AI799183, AW238688, AI932966, AI354643, AW168788, AI401697, AI357940, AI890214, AW078712, AI250627, AI636507, AI357273, AI634345, AI579901, AI352497, AV711455, AW104724, AL514079, AI783825, AI612852, AI956080, AI524654, AW104827, AI445025, AI815232, AW198090, AI684244, AL513761, AW078606, AW083374, AA830709, AW192652, AK001356.1, AF260728.1, AL137599.1, AK001651.1, BC008337.1, AB033000.1, AF351620.1, AF18393.1, AL389935.1, BC003573.1, AK026408.1, AL117587.1, BC008591.1, AL080159.1, BC006103.1, AK026462.1, AL137530.1, BC002466.1, AK026744.1, AK026593.1, BC003101.1, AL133075.1, AL137537.1, BC005825.1, AK000418.1, AL136850.1, AL023657.1, BC001199.1, AK026389.1, BC004945.1, L19437.2, BC004349.1, AL122104.1, AL050149.1, AL389982.1, BC006181.1, BC001964.1, AB047878.1, BC002631.1, AL050138.1, AB050410.1, AB050421.1, BC006345.1, AK000414.1, S76508.1, BC008686.1,</p>
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HNFJY77	164	634551	1 - 1198	15 - 1212	BE778688, AA350580, AW451334, BE247283, BE242191, A1640492, AA078462, BE242141, AW003105, AA336368, R54889, A1910199, A1871293, A1267818, BF204188, A1858691, AC009412.6, AC072052.6, AL033517.1, AL161747.5, AC018897.4, AC005663.2, AL139095.15, AL135744.4, AC008072.3, AC005484.2, AL121897.32, AP000359.1, AC079141.7, AC020955.6.
HNFJF07	165	577013	1 - 602	15 - 616	AA487061, AA486615, D78759, AC002091.1, AC004089.25, AC005015.2, AC039056.7, AC006329.5, AC005081.3, AC084693.2, U91323.1, AC002352.1, U82668.1, AL391259.15, AL109897.30.
HNGDJ72	166	532619	1 - 510	15 - 524	AC027689.10.

HNGEP09	167	499076	1 - 1028	15 - 1042	AW275971, AI369580, AW576034, AL353692.14, AC004638.1, AC027319.5, AC007011.1, AL354932.26, AK000932.1, AC074121.16, AC019171.4, AL390374.16, AJ400877.1, AL158830.17, AL109897.30, AC008403.6, AL121929.17, AC016025.12, AC002390.1, AL360227.17, AL049709.18, AL353777.18, AC004890.2, AC005098.2, AC005015.2, AL354794.16, AL590762.1, AC020931.5, AP001695.1, AC005052.2, AL121754.18, AC073655.26, AC004166.12, AC005225.2, AC010328.4, AC004876.2, AL133353.6, AP000553.1, AL136418.4, AL139054.1, AC004985.2, AL354873.19, AL121897.32, AC003962.1, AL121972.17, AC011472.7, AC011462.4, AC073316.6, AC079602.15, AL590763.1, AL023575.1, AC007216.2, AC005049.2, AL139095.15, AC005033.1, AD000092.1, AL133453.3, AC011514.3, AC008072.3, AC009123.6, AC006130.1, AC005899.1, AC005800.1, AC016995.4, AL021368.1, AP003439.2, AC005740.1, AC004893.1, AC013726.7, AC007546.5, AL031727.42, AL109984.14, AC005280.3, AC020629.6, AL445490.6, AP000067.1, AC003010.1, AP000506.1, AC004520.1, AL121586.31, AB043547.1, AP000501.1, AC007030.3, AE006467.1, AC012476.8, AL512347.14, AC010203.13, AC004217.1, AL133387.8, AC051619.7, AC002504.1, AL096791.12, AL133347.28, AC004826.3, AC004910.1, AL031663.2, AC006544.19, AC069282.6, AF111168.2, AC005089.2, AC002551.1, AC020908.6, AL022323.7, AC011443.6, AC005914.1, AF001548.1, AC010271.6, AL049569.13, AC079630.18, Z93015.9, AL133246.2, AL356299.16, AC002984.1, AL121658.2, AC006088.1, AC006349.3, AC006125.1, AL096840.25, AC005971.5, AB000882.1, AC005519.3, Z93241.11, AL031447.4, AF196969.1, AC007686.5, AC005041.2, AC016587.7, AC009144.5, AC010618.7, AC009137.6, AL121903.13, AL512378.7, AC024028.10, AL117381.32, AC008392.6, AP003357.2, AL137162.25, AL139317.5, AC004626.1, AC006329.5, AL139396.17, AC007956.5, AC020552.4, AL139352.16, AC003065. 1.
HNGFR31	168	553552	1 - 522	15 - 536	AL360297.12, AC005023.1, AC022124.5, AC008390.7, AC004836.2, AL136984.20, AC009558.14, AL117373.14, AP002350.3, AC006265.1, AC007057.3, AL139233.8, AC005079.6, AL359824.17, AP001541.4, AP000426.3, AJ239322. 3.
HNGIJ31	169	519120	1 - 782	15 - 796	AU147901, AA376128, BE562634, AC051619.7, AC020629.6, AL445531.10, AC009412.6, AC005052.2, AC079383.17, AL009172.1, AC016637.6, AK022380.1, AC004032.7, AP000555.1, AC009789.21, Z83851.17, AL359643.27, AC011005.7, AC008521.5, AC008635. 6.
HNGND37	171	839224	1 - 827	15 - 841	AA774312, BE670568, AI298480, BE702731, AI088824, AI149772, AA976633, AI870274, AA010606, AA010607, AW957725, AA010628, T33898, T75431, AI355909, AC005300.10, AC006946.20, AF307451. 1.
HNGOI12	172	1041375	1 - 2114	15 - 2128	AJ006345.1, AC005950.1, AC003675.1, AC001228. 1.
HNHEU93	173	634851	1 - 734	15 - 748	AW502688, AW410844, AI444575, AW504667, AW157128, AV758849, AW974923, AI038029, AA533011, AW021674, AW731858, AA618531, AA554289, AA557945, AA046906, AI065031, AW963552, AL121039, BG180320, AI702049, BG059139, AA157876, BE080768, AI567676, AI745666, AV732057, AW953437, N72678, H53546, AL044966, BF942991, BF679568, BF724416, AI003068,

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HNHFM14	174	664507	1 - 283	15 - 297	
HNHFR04	175	646709	1 - 1667	15 - 1681	
HNHNB29	176	895462	1 - 1880	15 - 1894	AI049955, AA904211, AI921765, AU146342, R98218, BF725178, BF337320, AA515728, AL524675, BF772474, BG057207, BE675681, BE063437, BF804385, AI962030, R74433, BF724699, AV656063, AI499954, AI653776, AI523074, AI362442, AU118374, AW023302, AW957372, BE150793, AV763026, AV763058, BE281645, AW410354, AL038842, AW963444, AW403829, AA503298, AI709307, AW023111, AA825827, AV756491, AU158454, BF877926, AA713705, BG236484, AI735609, AW082104, AW780190, AV760014, AI254779, AA558404, AV719392, AA502532, AI114704, AA833875, AA833896, AA832145, AW957600, AA644090, BE072475, AW575605, AV703785, AW503420, AW973992, AI802087, BE301610, AW302017, AV738383, AW237905, AI859438, BF760573, AW962611, AV733437, BF944736, AV647070, AW513789, BG110818, AA581247, AI687343, BF854308, AW970958, AW615560, AI755057, AU157093, AI821987, BG222875, AA714110, AI732869, AA811741, AW849714, AL079734, AI889995, AA452887, AW978041, AV740009, AV764259, AA084609, H63660, AI587349, AW965008, AW190484, BE677244, AW501542, AW236219, BF217723, AA056248, AW843204, AV695478, AA633875, AW978591, AW192373, AW957154, AA604831, AW303872, AI141130, BF977305, AA297776, AI160786, AU151428, AU150634, AW083934, AA613624, AW051819, AI961983, BE968477, AW510513, AI417469, AC084881.19, Y10196.1, AL357515.26, AC005736.1, AL139396.17, AL356415.26, AC006241.1, AC006121.1, AL590763.1, AL022316.2, AL096677.21, AC016597.4, AF053356.1, AC002996.1, AL158040.13, AC012320.6, AC013434.8, AL109843.25, AC009194.8, AL356020.3, AC002425.1, AL133448.4, AC020916.7, AC005081.3, AL161731.20, AC078846.2, Z83819.1, AC011247.10, AL139317.5, AL022323.7, U95090.1, AC007225.2, AC083884.6, D86995.1, AC020913.6, AL356915.19, AL050349.27, AC023425.20, AC034242.5, AP001705.1, AC008946.6, Z95331.2, AP002008.5, Z98752.16, AC005920.1, AL157838.24, AL135839.15, Z93023.1, AC002045.1, AC005522.2, AC010419.5, AC016655.6, AC008616.6, AP001718.1, AL161669.5, AL035684.25, AP001752.1, AC002369.1, U95739.1, AC026794.4, AC015982.9, AL121586.31, AC009087.4, AC026202.6, AC008733.7, AL133477.16, AC005015.2, AL023575.1, AC007685.2, AC008397.7, AC018644.6, AL137061.12, AP001922.4, AC011442.5, AC006430.22, AC008766.4, AL132639.4, AC018821.4, AC006334.3, AC002492.1, AL157372.18, AC002073.1, AP000501.1, AC011465.4, AC022404.7, AC018639.8, AL135783.6,

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HNTBI26	178	1310821	1 - 1368	15 - 1382	<p> AL117344.12, AL121975.9, AL136300.22, AC006337.4, AL157838.24, AL158040.13, AC006970.6, AC007488.15, AC000026.3, AC008687.4, AC018720.5, Z84487.2, AL445222.9, AL132855.4, AC006480.3, AL031286.1, AC004906.3, AF196971.1, Z83843.1, AC003043.1. I.  AL528533, AL520935, AL521290, AL515806, AL520965, BE293492, AL520936, AL515807, AW972854, AV753139, BG178370, BF968317, AL520966, BE780476, BE305183, AI678037, AW293248, AL521291, AI269883, BF978348, AA894746, AI493776, AA778869, AI424848, AA525497, BF307374, AA622403, BG109953, N21347, AI095265, BF792489, AL519236, AA564674, BE249905, AI268502, AA995849, AA894745, AI249680, AW087844, AI300762, N72839, AI244187, AI089147, AI368934, AI740804, AI339842, AW516709, BF315359, AI335796, AW192649, AW801578, N28008, AI095231, BF977145, BF977663, BF765528, BE778762, BE875935, AI951011, BF669511, BG033337, AW393151, AL519237, AW819092, AW393138, BE868896, AV691113, BE875559, AV693124, BF976999, BF690855, AI127890, BE293585, AW984556, BF994881, AW090182, W76593, AA362394, AI906642, BE741647, T57136, AW753803, BF813621, AA533658, BF882501, AI638644, AI370623, AI698391, AA806720, T49776, AW008226, AI568293, AI332957, BE393784, AI590043, AI954721, AW128834, AI364167, AI419826, AW166870, AI884318, AI685005, AI473799, AI699823, AI440239, AI956080, AI393038, AI889189, AI621341, BG119543, AW166583, AW105296, AI580451, AI634345, BE966496, AI619820, AI570807, AW834282, AI499570, AI500113, AI620864, AI684369, AI633125, AW983832, AW103928, BF752997, BF727091, BF761618, AI254731, AW087934, AI802542, BE964556, AI927233, AI538564, AI270706, AW148882, AI915291, AW152182, N21402, AL046466, AA019328, BF811804, AI678446, AI473536, BF669151, AA102339, AW130362, AI653402, AI869765, AI270183, AI613038, BE965129, BG122005, AI950729, AI540821, AI700358, AI266652, AI701097, AW004606, AW198090, AW262552, AI934011, AI282669, AI349482, AI612913, AW084873, AI125015, BE963426, AI695857, AI636588, AI610446, AI572096, AI689157, AW075671, BF812960, BF996654, AI799183, AI687127, AI866419, AI824688, AI866040, AI824576, BE895003, AI683563, AW029489, AI540350, AI499890, BE963355, AI951950, BF724420, BG251076, AI421149, AI567513, AI866469, AI932966, AW129659, AI474146, AI298321, BE275487, AI816306, BE961919, AI539260, AW243451, AL080011, AA878142, AI567769, AV720998, AI524626, AI096481, AI470717, BF814527, AW102794, BE963310, AI478723, AI800341, AW089726, AI912434, AI648509, AI499963, AI673363, AF086351.1, AL117587.1, AL050366.1, BC008591.1, AB056106.1, X78627.1, X99971.1, BC004945.1, BC005825.1, AL080159.1, BC001199.1, BC003573.1, AL080148.1, AL080146.1, AK027095.1, AL136752.1, AC004942.1, AB047627.1, X68560.1, BC004416.1, AL133619.1, BC006181.1, AL133084.1, AF044323.1, BC004373.1, AK027052.1, AK026408.1, AL133653.1, AL133559.1, AF126488.1, BC008063.1, AL136850.1, BC001236.1, BC002373.1, Z82022.1, BC005123.1, AL139099.2, AL162066.1, AK025350.1, AL110280.1, AB056420.1, BC006345.1, AB050431.1, BC002349.1, Y14314.1, AK026210.1, AL137682.1, AC006288.1, AF115392.1, AK026182.1, AL133062.1, AL162729.8, BC008708.1, AK026746.1, AL357195.1, AL050155.1, BC002849.1, AB047878.1, AK000484.1, AJ299431.1, L25851.2, AC016706.6, BC004349.1, </p>
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HNTBL27	179	545534	1 - 777	15 - 791	AL050149.1, AL137478.1. AW169270, BF475369, AL524823, BE903984, AL530691, BE536833, BG230736, BE881512, BF033804, AA716162, AW183635, AI188277, AI141766, AI624087, AW173452, AI129419, AI683124, BE903838, AI828817, AI308087, BE544869, BF061917, AW291854, BE880241, AW471490, AW615124, AA701470, BF447518, AW025680, BF094269, AW449210, AA315210, BG251005, AW504333, AI239598, BE697836, BE742666, AI284846, AI355748, BE899398, BG027544, BF352604, AW376334, AW376337, AW752527, AW194025, AI890712, AI565340, BC006846.1.
HNTCE26	180	1160395	1 - 2149	15 - 2163	BG252201, AV726464, AL529709, BE894106, AV726994, BF970560, BF132059, BF977798, AI703275, AW512938, BG164577, AL529708, AI767521, AI823746, BE220262, AA583438, AI143608, AW468337, AI949854, AV727138, AI620344, AI209187, AI630993, BG007081, AI004986, AI565892, AV715169, AI367983, BF056815, AW394003, R70620, BG007658, AA152183, BF381743, AA565300, AA088574, AA931697, AA995899, AI025252, AA297479, T84083, AW138535, H71679, Z45535, AA297478, AI865989, AA367654, AA150060, AA044326, AW338484, D29436, R24591, AI005551, H00983, H39751, AI669105, T83438, BF091777, AW138127, R21165, BF083909, BE934286, R76620, AA971307, AA745052, AW945769, AI554153, T84151, BE550213, H01724, AW051517, AW373316, AW373313, T89390, BF083903, BE541509, AA180271, AI263504, AF303588.1, AF140242.1, AL13390.7, AF056032.1.
HNTNC20	181	700627	1 - 1965	15 - 1979	BG179496, BG254440, AA573206, AI735586, BE326906, AA131359, BF668303, AI522318, AI376670, AW241377, BE350501, AA452451, AA131240, AW242329, AI540415.
HNTSY18	183	1041383	1 - 1797	15 - 1811	AW470226, BF058886, AI692966, BF058139, BE218656, AI281699, AI241829, AA613450, AC004877.1, AL137162.25, AJ400879.1, AC011551.3.
HOCNF19	184	835049	1 - 1104	15 - 1118	F02459, Z17835, AI264655, BE011950, AV729096, N77968, BF807259, AA658839, AI076081, AW804948, BF987026, AC008078.11, AP002898.1, AL157369.7, AP002392.3, AC010999.6, AL353581.14, AC007383.4, AL133551.13, AL161659.17, AL132772.14, L81392.1, L81391.1, AC005317.1.
HODDF13	185	684307	1 - 816	15 - 830	AC011245.8.
HODDN92	186	422913	1 - 1925	15 - 1939	BG116781, BG110501, BE150456, AI742087, AA453725, AI917507, AW769479, AI860142, BE326465, AI459289, AI860141, AW963123, BE646467, AA868553, AW872412, AW971193, AW277065, AI921333, BF576826, AI024689, BE466760, AI354470, AI005467, AW103830, BE045272, AI827987, AA442638, BF109829, AA813604, N28268, AA442648, AA563934, N63406, AA833517, AA663108, AA437299, AA632986, AA436880, N58885, AA812876, AA447794, AA442379, N58892, AW020895, AA522837, AA600372, AA229448, T78981, AA663178, AV693238, AI187977, AV696576, AI472712, AA229164, T85178, AW270324, AV683374, R64648, AA333708, AA703066, AW961515, BE093710, T78927, R64655, BF802058, R95914, T84294, AA551512, AA460220, AI916737, R31132, AA359583, AI217018, N56349, AI191725, BE835233, BE835385, T84796, AV741009, BE835410, AI084517, N83238, AW362842, AA247541, R31089, T91125, AA493776, BE818350, BE818352, AI253986, R31247, AW303285, N95696, BE708493, AA678297, AI003856, BE818343, N95562, AW024721,

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HODEJ32	187	835027				AI671275, Z69713. 2.
HOFMQ33	188	1184465		1 - 725	15 - 739	AL528504, AU121718, AI820674, T94707, AJ224741.1, Y13341.1, AC079145.3, AJ001047. 1.
HOHBY44	189	873264		1 - 2396	15 - 2410	AW604409, AI037867, AW604404, AW368603, AW151676, AW383192, BE966058, BE927254, BF431876, AI753734, AI754387, BE966055, AW044602, AW383224, AI041650, AW383194, AI750595, AW383164, AI884505, W52686, AW069006, BG256681, AW842507, AW956164, AI750594, AA600082, AW078795, AI753050, AI802788, AW190902, AI750578, AW957491, BF055368, AI041803, AI621183, AW631119, AI750577, AW383125, BF215485, AA599801, AW087935, N31127, BE966060, W51909, AI087351, W47324, AA071381, W48619, AA670070, W48852, N35377, AI752124, AI090390, W42791, W47325, N28395, N28453, BE963587, AI085102, AI678451, AA545734, W42884, AA373348, AI302125, AI910477, H80042, AA071138, AA669811, AW361415, AW069430, AA788723, AW069485, AW853798, AI940729, AI754608, AW580737, AA376403, BF508389, AA373673, H99469, AA373544, AW473621, BF881941, AI888605, AA373014, AI940705, AA373975, N27040, C01826, AA373298, AA112124, AA084001, BE140157, AI940795, AA372833, BE140143, BE140150, AW005943, BE140098, BE140177, BE140175, BE140179, BE140161, BE140145, BE140148, BE140155, BE140167, BE140163, BE140147, BE140158, BE140149, BE140176, BE140107, BE140146, BE140152, BE140144, BE140099, BE140102, BE140166, BE140116, BE140156, BE140173, BE933516, BE140174, BE140104, AW239511, BG108248, BE140160, BE140171, BE140105, AI521673, BE140109, BE140164, BE140172, AW806615, BF109257, AW138508, BF217716, BE140108, AI932934, BE140103, AA373557, BE140153, BE140117, AA344024, W25447, AW806557, AI537571, BE140162, C01953, AI476777, AW583945, AF110137.2, AL359060.1, AL359059.1, AF154054.1, AB032372.1, AF045800. 1.
HOSBY40	191	589431		1 - 1131	15 - 1145	BE465874, BE465890, AW418562, AW814995, AA721114, AC002543. 1.
HOSDJ25	192	854234		1 - 2200	15 - 2214	AL521533, BF966564, BG109192, BE621548, BG259805, BF666690, BF667661, BF185318, BF666019, BE621125, AI433432, AW963800, BE883279, BF028488, BF667980, BF196902, BF111775, BF667265, BF664922, BF966437, BF667218, AI277896, BF028500, AI401346, BF696865, BF698781, BG169528, BF696312, AW338135, AI280253, AA873621, AI435513, BE552077, BF699387, BF055949, BF697521, BE542555, AI277959, AA121788, AI961880, AW969937, BF478121, AW338124, AA528626, AW367010, R76478, AA101422, T62844, AI918990, BE167397, W72961, AA876737, R28131, BE176581, AA375127, BF332407, AI365181, W73131, T62693, W21429, N92911, BF570557, AI077290, AA127501, R66340, AI926197, C00153, AA813575, R28517, AI580500, AI222072, AI033269, AA758476, W86851, AV661704, AV725920, AV728997, AV704234, AV726624, AV655280, AV729378, AV708992, AV727787, AV709407, AV654908, AV660608, AV652001, AV656903, AV707541, AV706854, AV702117, AV726738, AV728733, AV708834, AV687035, AV697196, AV708704, AV659322, AV656478, AV698545, AV709314, AV708381, AV660728, AV691080, AV651955, AV703169, AV728518, AW952409, AV709660, AV729220, AV696866, AV726816,

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HOUQC17	193	429229	1 - 4698	15 - 4712	<p>AI810627, BF344199, BG056542, BG118486, AI126019, BE784908, AW954313, W07142, AA133346, BE047207, AV700629, AW163200, AI692832, BF589805, AW195344, AI755040, AW964293, AI890478, BE856510, BF370410, AW168050, AI985641, AI926525, AI369060, AI654583, AI571069, AU158513, AW167394, AI129429, BF244275, AW474740, AI887177, BF083290, AA993528, N91530, AI148739, BE925407, AW001362, AA022464, BF203604, AW194129, BF590332, AI144408, AI335849, AI342643, CI8560, AI089584, BE934752, AI128171, BF476695, AI889755, AA677116, AW613713, AW163724, AA011376, AI684137, AI953558, AI097021, AA029247, BF589929, W47316, AI129732, AI168616, N59612, H98678, AV725614, AI280406, AI160430, AW080654, AU156318, AA834490, AI368138, AW207161, AI690716, AA677837, AA031474, AW104712, AW474712, AI559164, AA662930, W92688, W35345, AA057170, BF759760, AI340202, AI569560, AI185000, AI199506, AA757215, N40523, AA151507, BF221465, R19976, W47201, AI769318, T86778, N95765, AA595069, AI128696, W92831, N29991, T95293, AA028027, AA903074, AA703651, W24878, AA918632, Z43925, AI027793, AA328867, AA634915, AW967361, AA846139, AW204001, AI537176, N27243, AI859558, BF437005, AI921704, AI040586, R13547, AI719476, H28325, AW630984, AI765271, AA987460, R76276, W23529, N36334, AI270245, H28326, AI160028, H27128, AA345812, AA368429, AA373718, AA011364, AI370696, AI537518, AA296523, H89564, R20636, T40492, AI827556, BF197787, AA807465, AL047040, T95373, AI686088, H89565, R20667, R76553, N88341, AI689182, AW150550, T36271, AI932695, N46572, BF993688, T39243, AA781059, BE933134, AW050514, C03600, Z41664, AA088617, AA904875, AA897320, BG055227, AW050517, T86685, AI648649, AA040690, BE767617, BF370964, AA031616, AA029035, AI369552, AU140483, T10738, R45078, AW150472, AI933450,</p>

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HPEAD79	194	520202	1 - 799	15 - 813	
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HPIBO15	195	1310868	1 - 1725	15 - 1739	
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HPJBI33	196	685699	1 - 1663	15 - 1677	



					AL160271.19, AL157882.5, AL022323.7, AC018751.30, AL121900.26, AL356354.10, AL121897.32, AC006435.7, AL160471.5, AC027689.10, AC004878.2, AL121903.13, AL121890.34, AP000044.1, AP000513.1, AC004662.1, AC027319.5, AC011236.8, AC008738.6, AL136980.5, AC020904.6, AL132640.4, AC009516.19, AC018506.4, AJ400877.1, AC003003.1, AC016587.7, AC004847.3, AC012476.8, AP000555.1, AC020931.5, AC018719.4, AC003029.2, Z93241.11, AC004797.1, AL031281.6, AP001741.1, AC016894.7, AL033529.25, AC068533.7, AC011479.6, AJ003147.1, AL163248.2, AC022148.5, AP001727.1, AL031602.14, AC008403.6, AL139021.6, AC005488.2, AC006329.5, AC079602.15, AC020754.4, AC005736.1, AC004841.2, AL022316.2, AC003684.1, U47924.1, AL031733.3, AL365225.12, AL356915.19, AC008622.5, AC008073.4, AL050349.27, AL353135.32, AC005231.2, AC004707.1, AC022083.6, AL121585.22, AC005015.2, AL137800.12, AC016025.12, AC010616.5, AP001726.1, AC027644.9, AC034198.6, AC005295.1, AC007956.5, AL139321.28, AC006050.1, AC069262.24, AC013434.8, AC004382.1, AC010553.6, AC006581.16, AC004638.1, AE006463.1, AC007739.2, AC007011.1, AL049537.48, AL049760.26, AC006211.1, AF109907.1, Z93015.9, AC011462.4, AC090710.16, AC005844.7, AC006312.8, AC002990.1, AC008474.7, AC011489.6, AC007272.3, AL136418.4, AL139054.1, AL136137.15, AL139352.16, AL109936.10, AC002365.1, AL353579.17, AC005080.2, AL355302.14, AP001710.1, AC009298.3, AC004858.2, AL035404.20, AC005531.1, AC008812.7, AC011491.5, AC024028.10, AC004089.25, AL035659.22, AL354932.26, AC005529.7, AC007226.3, AC006452.4, AB050050.1, AC005837.1, AF111168.2, AL109797.18, AL135838.5, AL355392.7, AL021155.1, AC005512.1, AL009181.1, AC009137.6, AC004491.1, AC018720.5, AL445686.14, Z97054.1, AC007686.5, AC023344.4, AC011005.7, AC007597.3, AC005562.1, AL133367.4, AC010618.7, AP000347.1, AC002369.1, AC004953.1, AC010654.8, AC005081.3, AC008946.6, AC025540.7, AC011495.6, AP001748.1, AL049869.6, AC011461.4, Z86090.10, AC002470.17, AL138724.12, AC009412.6, AC005840.2, AC008760.6, AJ009611.6, AC008985.6, AC011484.4, AC015982.9, AC002133.1, AL049709.18, AC011444.5, Z98200.8, AC010969.11, AL121652.2, AP002851.2, AC008372.6, AL022320.23, AL109965.34, AL096701.14, AL031584.1, AC018809.4, AJ400879.1, AC018808.4, AC008616.6, AL034405.16, AC016643.6, AC005077.5, AC008649.6, AP000045.1, AL355305.9, AP001610.1, AC005225.2, AL161626.20, AC020908.6, AC073542.4, AC023510.16, AC006538.1, AC008764.7, AC012170.6, Z85996.1, AC003070.1, AC005778.1, AC022384.4, AC005037.2, AC020550.4, AL137140.12, AC004859. 2. AP001206.3, AP001329. 3.
			1 - 2634	15 - 2648	AP001206.3, AP001329. 3.
HPJBK12	197	1011467	1 - 2634	15 - 2648	AP001206.3, AP001329. 3.
HPJCL22	198	1146674	1 - 3093	15 - 3107	AU140137, AW273142, BF511622, AW500031, AW997852, AW997845, AW997846, BE263631, AW997843, AI457507, AW449421, AW451219, BE047152, BF946370, BF439925, BF946380, AI200349, BF897509, BF512501, Z19075, BE827516, BF094042, BF094020, BE244735, AA325330, AW962065, R31240, AI023715, AA736958, BF802328, BF988285, BG015997, AA215423, BF736763, AW997844, AA285156, AI254765, BF902055, BF724699, AV740801, AA847952, AA634889,

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HPMDK28	199	846357	1 - 1070	15 - 1084	<p>             BG112660, BG025264, AL528310, BG168817, BE744551, BE877617, AI356771, BG163540, AA203523, BG031683, BF822950, AW592567, AA176981, AA904437, BF209639, BF312400, AU134583, BF194783, BF058517, BF445932, BF115227, BF732680, BF445936, AW303381, AW149649, AW027536, AW583459, AW475091, AA065227, BF869433, AW103970, AA703536, AA902103, AI735312, AI082224, BE262098, AW405660, AW009422, AA932869, BF940753, AI830877, AI830074, BG222176, AI742006, AI381584, AA133474, AI347025, BF869417, AI452483, AA993536, AW954279, BE737248, N66683, BE261151, AI369439, AI334008, AI005081, AL528309, BE166345, AA365303, BF222033, F32952, AI697441, AA488152, AI418548, BG248769, AI279351, AI888277, BF115544, AI200343, AA977299, AI612818, BE163359, AI830668, BE740423, AW574601, AA315546, BE397815, AA573402, BE004351, AA573411, AA633508, BF925742, AA741489, H82686, BF894571, AA065233, AA360707, AV728079, BG230581, N29979, BE561199, N98991, AW439071, AA744699, R73710, AW407745, AA877633, H99709, BF804312, AI381618, BF806994, BF806622, BF806680, BF807000, BF807012, AW407070, BF804328, BF807005, AU155517, AA933001, AA321772, W57549, BF806996, BE271504, H39645, H26855, BF807004, H82425, BF804308, BF975948, AI928746, R81659, R82397, BE791088, R73635, BE939764, AI688429, BE171442, BF378561, BE261882, BF818292, AA469038, AA913203, AA300974, BE171441, AA298641, AW999308, BF206994, BF807016, H26756, BF093709, AW884799, BF737549, AW797205, H11203, AA305598, R81461, BF773046, BF804289, AI738864, BE814697, H49134, H40077, AW889970,           </p>

HRABA80	201	882176	1 - 1237	15 - 1251	<p>AI669504, BE561022, BE394911, AA911419, H40072, BF806979, R82344, AI701370, AI984879, AA064931, AI300423, AA380950, AI301586, BE902194, BE707909, AI983746, AA533457, AW803830, AA737402, AI926327, AI263788, R52293, F26866, AA827751, BF868527, AI168033, AI265814, AI264365, AW085104, AI982777, AW590204, AI381485, AI972009, AA580064, AA463767, AU130766, BE673288, BF109947, AA364441, BE464383, AI693626, AA133473, AW410601, AI685572, BF437257, AI279199, BF437797, BF064139, BE080941, BF059063, BE671687, AA064925, AI051392, BE348682, AI457365, AW341328, AW408516, AA622272, AA642661, Z21606, AA732692, AI261971, AA976709, BF091789, AW002951, BE163143, AI697458, T25507, AA341138, N86893, AI951605, BF058146, BE270120, BC008070.1, AK001809.1, AF277178.1, AK023110.1.</p> <p>AU147250, F24079, AI791459, AI732503, AA523577, AI791342, AU121439, BF309840, BF308519, AI659402, AA719317, AA602233, AI752815, AW967109, AV694013, AA470486, AI218622, AA644545, AK022184.1, AC005777.1, AL031431.8, AC007406.1, AC032011.14, AC004143.1, AC006131.1, AC074121.16, AC005760.1, AC005529.7, AL354766.17, AC025166.7, AC012476.8, AC005544.1, AL035079.14, AL356299.16, AL031297.4, AC005778.1, AC011666.28.</p>
HRACD15	202	871221	1 - 1525	15 - 1539	<p>AL519765, AL519766, BE910445, BF684654, BE270497, BE513843, BF975936, BE396890, BF973472, BE515166, BF686665, BE744708, BG257119, BE880162, BE797305, AW248552, BE514176, BE793786, BE791776, BE296702, BE271500, BE268991, AW512838, BE791090, BE727326, BF026627, BE797018, BE275277, BE277906, AU133849, AW248687, AU120611, BE270509, BF027092, BE384166, AI565668, BE513807, AW405789, AU151587, AA261853, AW043669, BE729554, AI949119, AW575486, AW751019, AI524253, BE391940, AW245114, AU145208, BE312276, BE796133, BE561087, AI953094, BE390017, AA283855, BE265439, BE391036, BE391843, AI620547, AW402545, AI075157, AI744741, BF125945, BF941740, W60104, BE266246, AW085553, AW131075, AI768378, AA401964, BE390215, AI752668, BE736619, AW967867, AI565659, BE387591, BE222775, AA283856, AW750999, AA261854, AI498229, AA830894, W60024, AA496293, AI660481, BE960924, BE277521, AA994223, AA868400, BF026241, BE382766, AI801124, BE671092, AI264882, AI355420, AW248994, BE503489, AI262893, AA583344, BE266582, AI832018, N29665, AA622755, AI439625, AI193362, BF446254, BE504260, BE387503, AW806699, AU146635, BE856089, AI087826, BF801189, AA133817, AA843858, AI287716, AA928793, AA699788, AI027345, BE728607, AW629986, W52804, T10369, AW103963, AA933691, BE138812, AI284845, AW264928, AW152071, AI265798, AI809041, AI038469, AW246086, AI435409, AV691151, AW957437, AI620834, AI452870, AI860541, AI475835, AI418409, AI744163, AW002187, AV692842, AI521647, AA845397, AI744800, AW002140, AI309558, AU118709, W96176, AW768771, BE207457, AW236670, AW264115, D29066, AA026580, AA135589, H55790, AW732194, BG006063, AI024919, AA256768, AI214884, AA280734, AA565467, R87509, BF056311, AA643222, AI024305, BF204467, AA077296, BF310268, W07856, T30234, R48997, AI435115, AI567828, AI537884, AW050631, AI740587, BE162565, BE149783, AW090152, T10368, AW627586, AI537596, AA622914, T50404, AW016161, W45022, AI274609,</p>

					AA570075, AL039562, AA827726, AW246353, W04715, H89133, BF125722, AA626654, AW246566, AW519242, AI659744, AI752669, AW247535, AA077415, AW129363, AI202252, AA628809, BE869982, AI208476, BE206952, AW511835, AA037397, BF828156, BG031018, BE513491, BE736901, AW149144, AI189756, AA078651, BE513973, BF194732, H47888, AW954928, AA806404, AW080710, BF847605, AA077110, AA319080, AA101354, AI214676, AA434187, AA932091, BF837875, BE140453, AA428843, R11194, AA778244, AA077601, AW082443, N90686, AI675644, BF794477, W05073, AI520907, AL046053, AW298462, AA496322, T50535, BC008084.1, AK001129.1, AK021688.1, BC007488.1, AL117583.1, AC006014.2, AB014518.1, AC005488.2, Y16704.1, N54250, N81046, AA036807, AA135546, AA236044, AA262692, AA938381, AA204918, AA402082, AA455506, AA455507, AI217271.
HRACJ35	203	877666	1 - 2063	15 - 2077	BE906771, BE218907, AI912661, BE670671, BG166321, AW167740, AI698131, AI796048, BF476110, AW952474, AW474992, AW149683, AI814137, BF436724, AA452391, AI635719, AI422285, AI675301, AW301634, AI800309, AI023300, AI269915, AA054467, BF062213, AI220479, AA991181, AI159765, W88683, AI623293, AI205308, AA043330, AA461136, BE669608, AI032982, AA634903, AI361429, AA877688, BF681677, AW868366, AI683625, AI094869, AI268543, AI040482, AA460833, AI042583, AI800329, H40189, AA041196, AI420048, AA127006, AI023081, AA045134, T96696, M79132, W23483, BF000996, AI161385, BF476853, AI521085, AI984382, AA492294, AA016124, N95081, R13864, AI146307, W28330, AI022619, T19296, AA410735, BF573582, BF056915, T30952, AI971069, AA043329, AA126627, AA215786, R07660, BE833878, BE833866, AA329616, BE833882, BE833868, AA977851, Z41866, AA226105, AA126801, AA056673, AV693019, AA216384, R18560, AA041433, AW244035, R05716, AA868767, BF222351, H40140, AW589719, AV686312, BF207973, AA226035, AA228673, AI817777, AI420271, AV747189, AI248289, R05717, T30818, BF847400, Z38161, AA879250, D57208, R37006, AA319785, AI699205, T96591, AW945698, AA225132, AA333327, AA045610, D57177, AA226695, AA045355, BE905736, BE670421, AW469919, BF000980, AW771589, BF871391, F19153, AW152062, AW964837, R41427, BE242459, BF445505, AW373047, AW069103, W88670, AA761464, BF844537, AF107834.1, AF119386.1, AP003117.2, AF107833.1, AP003111.1, AP003112.1, AP003477. 2.
HRGBL78	204	910133	1 - 2094	15 - 2108	BE271199, AW575245, BF794609, BF797900, BE559773, BE384088, BE513826, BE270971, BF572042, BE560978, BF690655, BE674800, BE275832, BF303959, AW205367, AW402801, BF203242, AW402242, AW402928, BF305905, BE466652, BE892536, AW403946, N24246, AW968460, AI654541, N28316, BF572179, N29315, N38941, AW383418, AA458944, AI276242, BE729612, AA215300, N33010, AW383426, AW383396, N20230, BF692515, AI439520, N29316, AA459158, N25452, W03476, AW383428, AW402824, N30453, N28949, N21241, AI760983, N20533, AI434284, BG025865, N72999, N20563, BF896859, AW403434, N67502, AI470743, N73074, AA837208, AW407871, H84381, AW404443, N26470, W02963, AI864746, N46511, W02298, H98912, H84382, N35519, H99497, BF890914, AA761778, N71796, AI222330, BC006521.1, AL359541. 11.
HROAJ39	205	1181699	1 - 1132	15 - 1146	T66247, BE081925, R34513, F12057, AA852760, AA125904, BF996914, BF107281, BF743278,

HROBD68	206	827306	1 - 1984	15 - 1998	<p>BF742834, AB040901. 1.</p> <p>AI921101, AW102963, C17730, AW139132, AI499286, AU157470, AW157413, AW517766, AI285660, AL038713, AU146974, AA779937, AW272376, AI862212, AI246569, W58428, AU145383, AI051341, AI925647, AI869945, N77920, AI591332, AI440018, AU148220, AI872191, AV695638, T06365, AI310239, AI559442, AI818151, AA811111, AI453790, AA130476, F16040, AI685116, AI610326, BE646447, AA166854, AI540098, AI375417, AI887321, AA767353, AV693309, N20521, AI369914, AA846188, H96719, AA961590, AI088245, AA902828, BF112065, AA129986, AI439415, N30146, AI817158, N33132, N31608, AW084901, AA055654, BE245707, AI619818, AI628308, N20064, AV726924, AA347740, AA932087, AA657353, AA550798, AI028382, AW262471, AI147839, AA132716, AA460715, AI250812, H97388, BG027070, AW072619, BF002501, AI568919, Z36956, AI538654, N90055, AI376849, AI952804, AI264673, AA468571, AA584498, H04879, AA342051, AI733728, BF963854, AW962610, AA099788, AI858607, AI189033, AA157033, AI675848, AA722562, AA659014, AW468555, AA862135, AA911409, AA226507, AI244642, N24958, AW085676, AA169142, AA364962, AA569918, BF221900, AU156129, AV702748, AA016272, AI601265, AW272291, AI082077, AI376984, AI377100, AA864823, W16525, N26697, AL110383, AW088343, BE264670, T48029, T69889, AA724610, W96522, AA826143, AW753399, AI827133, AI783731, AI598077, AA565911, AL523955, BE677100, BF772474, AV695478, BF576607, AU143935, AL521095, H20876, W31567, BF805088, R70883, AA136630, H01156, AI521525, AA503213, H68343, BG152386, AI890971, AC009623.6, AC008173.2, AC084881.19, AL161901.18, AC020892.7, AC020603.4, AC024341.9, AJ271735.1, AC002486.1, AC013719.8, AL109847.5, AL138965.10, AL137011.9, AL356962.8, Z99758.7, AC005798.10, AL163202.2, AC073200.6, AC004894.1, AL451083.5, AC004087.1, AC025040.7, AC015987.5, AL163152.4, AL353772.14, AL590043.7, AC002527.1, AC009483.3, AB045357.1, AC005885.1, AL360089.13, AC067941.7, AL163203.2, AL162500.15, AP002532.1, AL355581.14, AC006334.3, AL445383.5, AB000882.1, AC021017.4, AP003493.1, AC073964.3, AL139109.14, AC010252.3, AC009802.13, AC023842.5, AP002797.3, AC008109.6, AL050309.4, AL353650.5, AL442183.4, AC006043.1, AC010719.4, AF224669.1, AC012558.8, AL022153.1, AL121578.1, AC010747.10, AC003091.1, AP001691.1, AL049732.11, AL583822.6, AC073137.7, AC003051.1, AC009120.8, AC007102.4, AL512427.10, AC018616.5, AP000949.2, AC018468.4, AL355888.3, AL050329.12, AL035466.3, AL139110.17, AC003083.1, AC087431.2, AL159152.11, AC007773.1, AC008427.7, AL138703.10, AC079631.16, AL133370.4, AL109753.9, AL512310.3, AC019041.8, AL160413.7, Z82205.1, AC016831.1, AP001692.1, AF017104.1, AL157915.3, AL355365.10, AC000112.1, AC003012.1, AL392087.7, AP000077.1, AC025226.4, AP001683.1, AC006249.1, AC007000.2, AC004605.1, AL158158.14, AC005668.1, AC022467.7, AC006239.5, Z98304.1, AL359085.14, AP000506.1, AC007262.4, AC034245.4, AL450305.7, AL356005.9, AL163248.2, AC090527.3, AF001549.1, AC008014.5, AP001922.4, AC005213.1, AC025471.5, AC006287.1, AL121595.5, AC012491.7, AF241726.1, AC069543.4, AC022363.24, AF196972.1, AC005562.1, AC022274.5, AP002436.3, AC002456.1,</p>
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HSAWD74	207	460527	1 - 956	15 - 970	BG056446, N32720, AW152171, AA339555, AA076697, AA525291, AA380007, BE734992, AA077031, AA379882, BE047929, AA515728, AI282253, AA683069, AW275432, AW274078, AA533025, AI675615, AL040054, AA644090, AI345123, N42169, AW023111, AV756491, AI962030, AV758870, AW021774, AA602906, BG222564, BG222326, AV762454, AL048060, AA225406, AI879951, AA078830, AW514006, BE063437, BF725844, AI591299, AI590522, H68343, AA825827, AA559166, AW272294, BF213224, BE049095, AI344810, AA714011, AW502237, H63660, H24331, AA171400, AL449689, AI753113, F18888, AA282951, AV761486, AW193493, AA669238, AI557644, AI049868, AW631267, AA525331, AW117740, AA507623, AA862183, BE968744, BE677164, AW571963, AI433952, BF991881, AA701080, BF970107, BF212465, AA832175, AA470933, AW157128, AI343144, AW974751, AW338376, AW410409, AW844636, AW664505, AA827383, AV760014, AI745116, AI003611, AV683406, AW021154, AW501278, BE968477, BF991882, AI189682, AU124213, AI336637, AW572140, AA610644, AW963463, AA708322, AA489390, AI887235, AC004084.1, AC004951.5, AP000252.1, AP001711.1, AC006160.9, AP000031.1, AC022383.3, AC009131.6, AL354864.16, AL121900.26, AP000212.1, AP000134.1, AL031281.6, Z99716.4, AC009144.5, AC005015.2, AL137852.15, AP001207.3, AL035458.35, AP001753.1, AC026794.4, AL139022.4, AC009179.17, AL033383.26, AC090498.2, AC011472.7, AL162578.13, AL590762.1, AL117380.28, AF045555.1, AE006467.1, AC006088.1, AL096701.14, AL137881.12, AC011491.5, AC018828.3, AC005081.3, AC034193.4, AL110115.38, AB001523.1, AL023586.1, AL022237.1, AP000348.1, U91322.1, AL049591.12,

					AL133367.4, AC018808.4, AC091529.1, AC005666.1, AC011497.6, AL450339.5, AC004655.1, AP001718.1, AC005052.2, AC026866.8, AL136228.8, AC005793.1, AL139317.5, AL354720.14, AC004129.1, AL035461.11, AL161727.15, AF217413.1, AC007371.16, AL049539.21, AL008729.1, AC000353.27, AC003962.1, AC005940.3, AL158830.17, AF001549.1, AC004263.1, AC006441.13, AP000345.1, AC011811.42, AE006640.1, AL035086.12, AC004777.1, AC055120.5, AC002430.1, X02571.1, AC009477.4, AC006285.11, AC006597.2, AC018663.3, AC011479.6, AL139193.4, AC005692.1, AC009220.10, AC005907.1, AC007384.3, AC005049.2, AC004913.2, AC010328.4, AC005701.1, AC016025.12, U59962.1, AP003357.2, AC006345.4, AC006241.1, AL356805.5, AC004089.25, AC009247.12, AC005520.2, AC004910.1, AC027319.5, AC011495.6, AC008126.9, AC008521.5, AC005231.2, AC006449.19, AC002554.1, AL138720.19, AC011485.6, AL138875.8, AC008747.5, AC002994.2, AC003029.2, AC005291.1, AC006430.22, AL121712.27, AC078962.30, AL359082.16, AC004647.1, AC002429.1, AJ277546.2, AL133351.33, AL355102.5, AL391827.18, AL137140.12, AC004812.1, AC005098.2, AL390878.6, AL512883.5, AC090958.1, AC004883.2, AL135924.11, M12901.1, AL109984.14, AC018758.2, AL133477.16, AC012170.6, AC026185.3, AC005736.1, AC090426.1, AF283320.1, AC012499.7, AC011446.6, AC005288.1, AC005355.1, AC006581.16, AL162430.15, AL133500.3, AL109865.36, AC010271.6, AL445195.4, AC005005.1, AC003043.1, AL354815.10, AC083884.6, AC008755.6, AL021579.1, AL354935.23, Z81364.1, AL109925.11, AL139339.22, AC004876.2, AC020983.7, AF195658.1, AL022727.1, AC005598.6, Z93930.10, AC011480.3, AF312915.1, AC005220.1, AC074121.16, AL139123.14, AC010679.6, AC027124.4, AL157838.24, AC010205.5, AL049547.10, AJ300188.1, AL357972.18, AC002350.1, AL356095.11, AL162505.20, AL118502.38, AL022331.1, AC021016.4, AC008753.8, AC011890.4, AC005409.1, AC005516.1, Z97987.1, AC010458.5, AF053356.1, AC006111.3, AC007537.3, AC002133.1, AL390026.1, AC002319.1, AL137142.20, AP000555.1, AC005180.2, AL135838.5, AC024028.10, AL034429.1, AC007055.3, AC007298.17, AE006639.1, AL078633.32, AC066597.4, AC007766.1, AC010605.4, AC025280.4, AC005363.1, Z68870.1, AL162503.12, AP000501.1, AL355101.2, AC006208.3, AC010422.7, AC008752.6, AP000901.5, AC008569.6, AP000346.1, AL031121.5, AC005038.5, L78810.1, AC005839.1, AC005037.2, AL391374.9, Z83840.7, AC005911.6, AC004840.3, AL034402.9, AC005228.1, AL035464.20, AL355336.15, AL121920.21, AC025166.7, AC011465.4, AC005695.1, AL133448.4, AC007003. 4.
HSDFJ26	209	834619	1 - 1191	15 - 1205	AI770009, BE467511, AW593206, AA434584, AI767843, AA780308, AA563708, AA317400, AA433906, AB021123.1, AC005598.6, AF361936. 1.
HSDJA15	210	795252	1 - 1429	15 - 1443	AW864388, BF680896, BE220848, AI982565, BE967606, BE042914, AI215617, AA553540, AW864512, AL118801, Z45033, BF949835, Z40201, T87220, F09990, H11649, R38421, F07708, R55771, R45396, F04558, R41971, AI863613, T16890, AW051331, F03377, Z40771, AA188521, AI699582, F04949, H97413, AI784055, AW510885, AW136105, AW467042, AL046385, AI690813.

					<p>AW080157, BF724894, AI364167, AI288328, AW265004, BE907663, AI559752, AL514511, AW972273, BF345598, AL514409, BF968666, BF868489, BF997967, AI689096, AW827289, AI925164, AI922597, BE876976, AI683270, AI342023, AI049669, AL513977, AL514359, AI950729, AW198090, AI598017, BE538997, BG105381, AI359787, AW194014, AI432532, AW087837, AI824357, AI860787, AL515413, N25033, AI581139, AI370623, AW972279, BG167830, BG033608, AI952306, AL513729, AV750565, AI421662, AI568061, AI580027, BE964206, AL513913, AI933574, AL514493, AI524179, AI610671, AI925281, AI917428, AI499963, BE780955, AI628214, AL514721, AI341690, AI224373, AI538008, AL514015, AL515171, AI887163, AI932794, BE729304, AI872154, AI267454, AI677646, AL514357, BF811802, AI635528, AV682250, AI638644, AW084896, AI890907, AL514791, AW105429, AW081648, AI538850, BG111199, AI583670, BE965732, AI345415, AW089844, BG029709, BF970652, AW020397, AW268221, AI446704, AW263796, AL514455, AW301974, AI049923, AI909641, AL513693, AI357902, AL513863, AV682403, AI651609, AI612107, AI499570, AI471325, AI522052, AI440238, AW020328, AL513865, BG114304, AL513713, AV682366, BF037097, AI289483, BF751299, AF255922.1, AL109779.1, AL161964.1, AK025113.1, AL136825.1, AK024992.1, AL133084.1, AF369701.1, AB062978.1, AK000476.1, AK026038.1, AF232009.1, AL050366.1, AF339775.1, BC007460.1, BC009398.1, AB060884.1, AB063074.1, AK000083.1, AL162002.1, BC005805.1, BC004899.1, AF155656.1, AF326206.1, AF265236.1, BC004925.1, BC001967.1, AL359583.1, AC026307.16, BC009294.1, AL122110.1, AF002672.1, AK000653.1, AP001624.1, BC004292.1, AK027204.1, AL117460.1, AK025258.1, AK000718.1, AL389983.1, BC003591.1, AK025099.1, AB056421.1, BC001059.1, AK025092.1, AB047627.1, AL136805.1, AL133559.1, X68560.1, AP001746.1, AL133049.1, BC004349.1, BC005094.1, AL050149.1, U62966.1, AC002471.5, AC005374.5, BC008282.1, AK024747.1, AL133072.1, BC008591.1, AK026630.1, AL137533.1, AB060229.1, AC079801.2, BC009285.1, AF183393.1, AK025435.1, AL133608.1, BC005007.1, AL133088.1, BC007567.1, BC007420.1, X99971.1, S71381.1, AK027116.1, AF277181.1, BC004202.1, AL117435.1, Z35309.1, AK026633.1, AL117587.1, AL080154.1, BC005816.1, BC006458.1, BC002733.1, BC008649.1, BC001785.1, BC001964.1, AK026570.1, AL080150.1, AK025465.1, L10376.1, AL450164.7, AL137271.1, AK026885.1, BC004513.1, AL122100.1, AK027260.1, BC008387.1, AJ001838.1, BC007905.1, AL117626.1, AF143723.1, AF141289.1, AF103804.1, BC000100.1, AK024855.1, BC001305.1, BC002933.1, AL137548.1, AF090934.1, BC008364.1, AF217994.1, BC000090.1, S70057.1, AK024978.1, BC007796.1, M92439.1, BC003410.1, AK000418.1, BC006091.1, AL137560.1, BC008504.1, BC004951.1.</p>
HSDJM31	211	491112	1 - 547	15 - 561	<p>AA426010, AI986451, BE856226, AA773781, AI699994, BF477477, BF929123, BF526671, BF341281, AW020695, BF929118, BF966870, BF966816, BF966822, BF342126, AV726843, AC018616. 5.</p>
HSDSB09	212	1301498	1 - 795	15 - 809	<p>BF432333, AI861851, AI240993, AI795956, AI074484, AI640759, AW006868, AW241621, BF592070, AW271387, AW614840, AW450466, AW243423, AI244694, AI640517, BF431431, BF431530, AI439169, AI613108, AI915938, AI984796, AI245393, AW300335, AA931466, AW235983,</p>



HSHAX21	213	612823	1 - 1972	15 - 1986	AC005722.1. BE379784, AL522216, AL520172, BF439334, AI652855, AI766309, BF512139, AI635715, AW299533, AW299897, AI129966, AW411210, AI624534, AI925109, AI803484, AI804159, BF184613, AA279212, AI609083, AI969459, AI860837, AA879465, AI183591, AW104990, AW316983, AW474646, AW630619, AI955714, AW409582, AA678827, BE139077, AA766602, AI431314, BF087963, AA081236, AW194027, BF701425, AI521521, AA588351, AI923638, AU155980, N39554, AV686756, AA769352, R78080, AW613876, AA259257, R22218, AA443811, AA969814, AA729654, R80114, T60532, AI969030, AW572611, AA259256, R80005, AW805183, BF592136, T51990, BE972627, Z38832, R23587, R24524, T52102, AA371263, AI564179, AI783565, BF700820, BE619819, AA447188, AK001845.1, AL136705.1.
HSIDJ81	214	589447	1 - 1289	15 - 1303	H27567, H27494, H71543, AI754653, BF857849, AW023111, AI521525, AW572721, AW963450, AI254770, AI926102, AV701462, AW020150, AI871973, AW500534, AW275432, AA218851, AA595661, BF854170, BF853574, BF853009, AW151247, AA536040, AW274078, AW958962, AI791659, AA669238, AI223626, AI249853, AW302048, BF725844, AI284543, BE139139, AW855625, AL042621, AW575000, AI801505, N68677, AI250552, AV758870, AW272294, H86725, AW851405, AI625604, AI251034, AA525807, AW075979, AI697235, AI090377, AA570255, AA702637, AV760014, AA729387, AA831426, AI697239, AI697242, AW504224, AI879951, AW502949, H77492, AW514065, AI224583, AV759203, BF527070, AA491767, AA229496, AL158830.17, AC005412.6, AL355855.23, AL132718.5, AL391868.15, AF285442.1, U91321.1, AP000505.1, AF129756.1, Y14768.1, AB000882.1, AL353804.22, AC005013.1, AC004448.2, AL139415.10, AC009309.4, AC091529.1, AL391122.9, AC009996.7, AL354836.13, AC010530.7, AC005274.1, AC007242.3, Z98048.1, AL354861.11, AC006121.1, AC007685.2, AC020552.4, AC008126.9, AC090509.1, AL096701.14, AC090951.1, AC066597.4, AC068319.4, AC006581.16, AC005332.1, AL117334.29, AC005200.1, AC024163.2, AC005632.2, AL031447.4, AL163279.2, AL355074.5, AL121586.31, AL021546.1, AJ295844.1, AC005484.2, AC013717.8, AL445196.7, AC007255.4, AC008760.6, AL136219.17, AL160274.9, AL031277.1, AL390037.16, AL031658.11, AC012170.6, AC005102.1, AC026464.6, AF228703.1, AC008068.4, AC005921.3, AL121808.4, AC004699.1, AC009412.6, AL031311.1, AC007216.2, AB053170.1, AL109965.34, AC009488.5, AF312915.1, AL132713.11, AL133173.19, AC087225.1, AC022516.4, AC009314.4, AC007376.9, AL034420.16, AC007850.29, AC005280.3, AL449305.4, AC020913.6, AC010326.6, AL391259.15, AL512885.4, AC004824.3, AC024168.4, AC009137.6, AL023575.1, AC010271.6, AC011446.6, AC004000.1, AC090005.1, AL121594.6, AL031726.22, AC005180.2, AL136305.14, AC006251.3, AL139316.5, AC007262.4, AL109963.4, AC012085.4, AP000503.1, AC005995.3, AC007041.3, AL121903.13, AL139039.17, AL121973.2, AL022326.1, AC073101.7, AL359986.15, AC006449.19, AL356257.14, AC019206.4, AL358237.13, AL138720.19, AC006457.3, AL162458.10, AL034380.26, AP002436.3, AL445143.2, AC010223.5, AL157952.8, AC007707.13, AL031293.1, AC008641.6, AL357315.14, AC003080.1, AL138688.27,

					AL138752.5, Z95115.1, AL158207.15, AC004840.3, Y10196.1, AC005859.1, AE006465.1, AL356115.9, AC018492.6, AC006455.2, AC018764.6, AL117348.25, AL049835.3, AL118520.26, AC004491.1, AC005480.3, AC090518.2, AC010618.7, AC005940.3, AF111168.2, AP000213.1, AC018636.4, AL356299.16, AC091493.1, AL136179.15, AC005257.1, AL096791.12, AL139113.21, AP000135.1, AL357518.15, AL021808.1, AL133453.3, Z93017.6, AL365444.11, AL390838.26, AL445669.9, AC008812.7, AL513008.14, AC007537.3, AC004447.1, AC003029.2, AC026776.4, Z97054.1, AC005399.19, AC010412.7, AL133466.22, AL136164.8, AC005527.3, AP000031.1, AC010616.5, AC074295.7, AC090532.1, AC004846.2, AC018808.4, AP001724.1, AC005529.7, AC004551.1, AL353777.18, AC004686.1, AC008044.4, AC018663.3, AC004873.3, AP001412.2, AL022316.2, AF064858.2, AC008279.3, Z94801.1, AC010363.6, AL162390.9, AC005070.1, AL078596.8, AL590762.1, AC079177.21, AC003101.1, AC004644.1, AC006101.3, AC005516.1, AL353798.9, AC002037.1, AL049576.19, AC008784.6, AC011455.6, AL162584.9, U82828.1, AF134726.1, AC009319.19, AC007541.9, AL136295.3, AC013449.8, AL132780.5, AL109952.15, AC005081.3, AC007991.7, AF168787.1, AL136304.10, AC004789.1, AL354808.24, AC027130.5, AP000152.1, AL138958.18, AC020633.3, AC004813.2, AC018500.3, AC006077.1, AL109956.19, AL139317.5, AC004851.2, AF243527.1.
HSJBQ79	215	1304677	1 - 573	15 - 587	BE875623, AL520513, BE889141, AW239200, BE874464, BE245256, AV7233508, BF055054, A232452, AA853047, BE885254, BE185284, BE620276, BF772972, BF772971, AW068453, AW176526, AL520512, BF772807, BF809972, AF183423.1.
HSKDA27	216	1352409	1 - 4398	15 - 4412	BF338364, BG253437, BG122685, BF037455, AW303375, AW173315, BF037378, BG120262, BG117983, BF915045, BF057308, BG252401, BG034853, BF793365, AW379378, BF826037, AA570507, BF915582, BG122734, W07328, AA600736, AI971935, BE697573, BE313814, AI090486, AI751258, BE839359, BF447303, AW631492, AA625303, BF513067, AI609700, AI768270, AI751257, BE939504, AA417652, AI751036, BE378218, AI652363, AI971415, AA599207, AI371013, AA024968, AI147536, W55850, AA063585, AW794702, AA446024, BE889110, AI828437, AI862133, AA421744, AI272646, AI148235, AA419609, AW005418, AA634323, BF883408, BF378271, AA416767, AA258414, AW305114, AI083516, AI752526, AW024492, AI698032, AW957682, AI092202, AI191710, C05155, AA419525, AI218226, AI754332, AW794499, AA410929, AI936116, AI079893, BE272411, AA593295, AA455497, AI039656, BG035195, AA747741, AA774270, AA364833, AI350380, BF940413, T59268, BF197746, AI084698, AW800540, AA834031, AI673545, AW795817, AA978105, AA622501, AA032249, AA912802, AI432010, N66832, AI751035, AI754989, AI082183, BE178218, AI751086, N75819, N67061, AA971661, AA873147, AA478719, AA036654, T59227, AI538117, AA662437, BE765721, T66232, AI751085, AW674273, AA024662, BF197986, AI564218, AA319726, AA657729, N64555, AA852211, C03119, AI221431, AA455496, AA033678, C04206, AI520867, AA258397, AW867914, AW867908, AA382381, N24008, AA456579, AA936765, AI433202, AA446297, AW338252, BF940540, AI075349, D31528, BE839377, AI537292, AA382234, AI446798, BE839418, AA459088, BF724219, BE839363, BE773013, AI064722, AW375493, AW375513,

					<p>AW375482, AW375483, AW375502, AW370152, AW134700, BF352435, AW375514, F12285, BE772982, AW797394, BE839409, BE710069, AA299257, A1061637, BE773049, AW375497, H63649, AW805832, H29954, A1587210, AW836298, BE773047, H75893, BF985423, BF089372, AA610296, T73259, D30912, BE839372, BE934501, AW937287, AL531501, A1270416, AW376140, AW838930, A1886158, AA375571, AL134647, H94943, BG006581, AW964941, AA336003, AA410897, R94988, W47433, R64321, D31541, W39467, AV693669, T82080, W04350, AA384793, AW572523, BE693478, AW375499, BF569459, AA428478, BF001215, H43934, AA382233, Z20767, AA382380, BE157468, W16893, BE066790, AW384231, BE157596, H80974, R96403, BE814079, AA345211, BG153436, AV654605, BE157507, AW292030, H62182, AW384236, A1382511, BF674009, AA335755, H25902, W65400, BG169442, AV710284, T64640, AA994712, BF944442, BF725435, BF726055, BF917617, W67868, H71581, AA326037, M14036.1, X07577.1, M13690.1, M13656.1, M13203.1, X54486.1, X07432.1, AB062098.1, X07431.1, AB062097.1, AB062096. 1.</p>
HSKGN81	217	676075	1 - 1893	15 - 1907	<p>BG110811, BE745101, BE743722, BE545826, BE745120, BF681303, AW978606, AV702796, BE047756, BF848815, AW961578, AA446896, A1422823, BF848816, A1911304, A1038608, AA312710, A1143843, A1150244, BF829479, A1193547, AA705005, A1268239, A1140112, T65948, BE547522, AA393113, A1366477, A1085862, A1074853, A1277116, A1983894, AA394060, AA643650, A100891, BF819277, AA922511, AV762171, AA478086, A1689302, A1275103, A1359079, AA532473, AV729423, BE349933, A1287604, AA477628, AV704180, BF847512, A1921910, AW105712, AW370596, A1624549, AW149890, AA505962, AA321215, A1357856, AA292337, BE292730, T34097, AW439882, AA447016, A1914726, R42595, A1858704, A1446219, A1275944, Z43230, BE707350, AW194214, AA135290, AW378090, BE241555, BE243232, AA010669, AW953547, AA632244, AW662488, BG057144, AW068278, R12726, BE151809, AW674205, T74373, N78860, BE242323, T31535, A1689506, R27706, F09665, R17501, AA435604, AW572245, BE548954, A1023355, BE545268, Z41318, AA383547, AA454729, AA570630, AA031630, AW173762, AW840945, AA381001, AA234325, T35951, Z45645, BE242712, T35949, A1866536, AA381111, AA693741, D82426, U83555, BE243322, F12018, AW793087, D82527, T64523, AW130852, AW262657, AA090647, AA359844, T19865, AA082483, U52870, R39778, W17267, AW603488, AA858156, AW068025, AW801618, BE242609, R05679, BE672790.</p>
HSKNB56	218	548077	1 - 1320	15 - 1334	<p>AV715380, AV705910, BG170454, AW300598, AW996981, AA669095, AA278335, A1797687, A1948608, AA464762, AW996774, BF036901, A1718165, A1129358, AA504439, A1765613, AA114888, BE702298, AA521311, AA114887, AW298550, AA504203, AA810071, A1051218, A1299255, AA804200, A1701050, A1694270, A1631949, A974370, BF434357, A1890342, AA256836, A1129632, A1023212, BE709212, A1935316, BE702132, AV726168, BE702036, AA252310, AA831496, AA662808, BE169470, AA464174, D57415, AA705444, BE702013, AA280044, Z44155, AW902156, BE702163, T71333, Z25261, BE702070, D54675, AA165321, W46279, A1420451, N69756, BE702230, T71487, AA832206, AA973497, AA521314, BF109037, AA877638, AW196653, A1027401, AA255623, AA863081, A1807828, A1831132, AA995204, AA252340, Z28882, W46278, Z40146, BG249572,</p>

HSNAD72	219	467397	1 - 847	15 - 861	<p>D57019, BE549886, N87679, T84473, AA452985, Z19443, AI918466, AV651701, F00129, AV651262, BE841213, D56990, AI351209, BE813969, AW369458, AA743770, AL047888, AL047889, AW997000, BF840712, AW582764, AW963201, AW339489, AC002350. 1.</p> <p>AW971203, AW861646, AI610321, AI880774, AA829195, AI880765, AA551170, AI969833, AA133550, T61620, AV758870, AA557945, AW873417, AI635819, C06160, AV761107, BE268727, AA743968, AA845333, BF574331, BG222875, BF946125, BF882222, BE068993, BF946124, AA493841, AW169469, AI251576, AI821901, BE044000, AI701898, H86399, H47461, AI338426, AI926093, AC009086.5, AC003007.1, AF001549.1, AC004638.1, AC018868.4, AC008747.5, AC090527.3, AL050318.13, AC078846.2, AC006254.10, AL035462.21, AL355476.12, AC026431.3, AC087091.1, AC005245.1, AL031311.1, AL136981.22, AL391241.21, AC010422.7, AC010267.6, AC011609.9, AC006538.1, AC006483.3, AL353807.18, AL049776.3, Z98200.8, AC067722.21, AC010913.9, AC008622.5, AC018828.3, AL080317.11, AC005484.2, AC022383.3, Z97989.1, AL117258.4, AC004531.1, AL121594.6, AL161656.20, AL122020.5, AL157372.18, AC067742.5, AL021453.1, AL390074.17, U47924.1, AC005077.5, AC002404.1, AC008482.5, AL035404.20, AL136124.10, AC005519.3, AL359983.7, AC005932.1, Z74739.1, AL034402.9, AC004813.2, AL136304.10, AC007386.3, AC022392.4, AL136979.16, AL031660.16, Z83844.5, AP000279.1, AC004975.2, AC011462.4, AL139809.16, AL450226.1, AC007193.1, AC008812.7, AC025588.1, AL445212.9, AL121890.34, AC011497.6, AC008752.6, AP000688.1, AC007216.2, AL356915.19, AP000106.1, AF207550.1, AC016742.10, AC005620.1, AC022384.4, U95742.1, AC004000.1, AL117381.32, AC011479.6, AC007285.3, AC008484.5, AC005755.1, AL157838.24, AC023790.21, AL162724.16, AC011487.5, AC000353.27, AL137077.31, AL031733.3, AL445490.6, AC025165.27, AC018711.4, AL354707.17, AC006251.3, AP000038.1, AL590763.1, AF129756.1, AP002852.3, AC005602.1, AC010170.3, AC005041.2, AL050302.2, AC005821.1, AC004846.2, AC003041.1, AL133238.3, AL031575.1, AC005257.1, AL137918.4, AC007163.3, AP000555.1, AL135905.6, AC020915.6, AP000047.1, AC025280.4, AL117330.6, AL135927.14, AC007227.3, AL049868.20, AL133367.4, AC007686.5, AC005365.1, AC006511.5, AL163203.2, AC020928.6, AC007298.17, AC009756.9, AC005666.1, AL359091.10, AC006515.7, AL139353.3, AL136170.12, AC009238.4, AL353804.22, U91323.1, AL160236.4, AL450224.1, AL159997.14, AP001724.1, AC006452.4, AL158830.17, AC004812.1, AC007751.3, AC004675.1, AL080243.21, AJ246003.1, AL354932.26, AC009488.5, AL391987.15, AP000213.1, AL354935.23, AL158813.16, AP000744.4, AC002543.1, AC010271.6, AL138878.10, AP000558.1, AC009144.5, AL020997.1, AC004913.2, AC008392.6, AL133246.2, AL161436.12, AC073073.2, AC012306.11, AC020914.7, AC090942.1, U52112.1, AL110115.38, AC004491.1, Z96074.4, AP000135.1, AC005410.2, AJ009616.3, AF165926.2, AL121886.22, AL109628.5, AL109743.4, AC008760.6, AL078477.5, AC004534.1, AL357052.15, AC006077.1, AC008745.6, Z98752.16, AP000692.1, AC009077.7, AP000031.1, Y18000.1, Z98051.6, AC002418.1, AC008687.4, AC005920.1, AC004234.1, AC012476.8, AL513043.7,</p>
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HSQFP66	221	460537	1 - 463	15 - 477		BE465277, BF593260, AI765036, BE181153, BE181155, AA834498, BF365438.
HSRFZ57	222	892171	1 - 1916	15 - 1930		AC006159.3, AF125348.1, AC084730.2.
HSUBW09	223	413246	1 - 1007	15 - 1021		AI991103, AI765351, AA703513, BF939824, AI925701, AW295389, AW976578, AI199421, AI422698, AI934983, BE501421, AI127932, AA703493, AW297092, AA677025, AA848037, AA814098, AW404152, AW904298, AW182186, AW197850, AA741121, AA651794, AI678148, AA906044, F18680, AA743764, AI632270, AW590435, BE045258, AA608892.
HSVBU91	224	596868	1 - 713	15 - 727		AW839808, AA077633, BF919965, AC008171.3, AF041056.1, AC004089.25, AC005081.3, AC005015.2, AB006629.2.
HSXGI47	225	886200	1 - 1242	15 - 1256		AV760760, AW968156, AA737309, BE88245, AA640430, AA167792, AL163279.2, AC019205.4, AC027319.5, AC011811.42, AL449363.12, AC011445.6, AC020916.7, AC003663.1, AL162615.13, AL121886.22, AC005412.6, AL096840.25, AC007404.4, AL035704.9, AP001717.1, AC005098.2, AL356915.19, AC003029.2, AE000658.1, AC007739.2, AC010359.5, AC004867.5, AL022476.2, AC083884.6, AC005512.1, AC009079.4, AC004965.2, AC005932.1, AL031670.6, AC022217.5, AP002852.3, AC010605.4, AP001725.1, AC011489.6, AC008736.6, AC005519.3, AC009123.6, AL590762.1, AC004983.2, AL049776.3, AL138756.23, AC004166.12, AC008744.6, AC008474.7, AC005011.2, AC008812.7, AC011005.7, AL034420.16, AL137792.11, AC074121.16, AC016643.6, AL355392.7, AL121594.6, AC005089.2, AC020913.6, AL022721.1, AL449305.4, AL109827.8, AC006023.2, AC018720.5, AL035685.21, AL021155.1, AC010102.3, AC007731.14, AC079468.3, AL008730.1, AP001724.1, AC005666.1, AL391803.14, AC005736.1, AC020908.6, U91323.1, AL121845.20, AC005000.2, AC008745.6, AC008537.5, AL031005.1, AC026464.6, AL031727.42, AC011446.6, AC027644.9, AC008555.5, AC004821.3, AL031311.1, AF001548.1, AC009220.10, AC005280.3, AC016637.6, AP001716.1, AC011491.5, AC004491.1, AL022328.21, AC0090947.1, AL135749.3, AC006141.2, AL354760.11, AL035659.22, AC027126.4, AC005102.1, AC020663.1, AL022323.7, AL050318.13, AL022322.1, AC008379.6, AC009155.3, AC011485.6, AC016644.7, AC008895.7, AC000353.27, AC005484.2, AC005274.1, AF053356.1, AL135927.14, AC007227.3, AC005500.2, AC008521.5, AC009144.5, AC007318.4, AC005288.1, AL161670.4, AC011461.4, AL133367.4, AC010320.9, AL022315.1, AC005800.1, AC002418.1, AC006101.3, AL391259.15, Z93023.1, AC006014.2, AC002350.1, AC009570.13, AD000092.1, AC007003.4, AC009131.6, AC018828.3, AC004929.2, AL138724.12, AL079342.17, Z99716.4, AC002425.1, AL121992.24, AL096791.12, AL049874.3, AL049759.10, AC005527.3, AC004883.2, AC018711.4, AL118520.26, AL121653.2, AC025593.5, AC006452.4, AL050335.32, AL139317.5, AL117348.25, AC006441.13, AL390252.9, AC019206.4, AC007151.2, AC010530.7, Y14768.1, AP000113.1, AP001709.1, Z93015.9, AC000003.1, Z84466.1, AC006329.5, AC004841.2,

					<p>AC002312.1, AC018638.5, AC006345.4, AC002565.1, Z83844.5, AL451075.15, AC007374.6, AC005821.1, AL356481.16, AC004967.3, AC005071.2, AC009412.6, AL139113.21, AC011247.10, AP000505.1, AL121819.6, AL033529.25, AC008738.6, AC003070.1, AC018809.4, Z93017.6, AF317635.1, AF196779.1, AC074013.5, AF129756.1, AC009120.8, AC008547.5, AC009086.5, AL034429.1, AL158830.17, AL353777.18, AC008481.7, AP003439.2, AP001748.1, Z95116.1, AC005057.2, AE006639.1, AC009309.4, AL355312.24, AC004951.5, AC009137.6, AL020997.1, AL049569.13, AL158206.8, AC026765.22, AL133174.15, AL445686.14, AP002348.3, AL160165.17, AC016526.6, AC068533.7.</p>
HSYAZ63	226	1177537	1 - 3452	15 - 3466	<p>AV722966, BE388876, AV760983, AV762946, BF185935, AV762161, BF108823, AV759946, AV761323, BF064074, BF689470, BF001385, AI970338, AL046433, AI348109, BE349503, AI819289, AI090048, AW305162, AI857825, AA551911, AI963412, BF690404, N90883, AI652494, BG055077, AA311166, BE502539, AI200346, AA158746, AA502649, AW083258, BE551410, AV763075, W04340, AA150467, F29360, BF436259, AA040295, F21409, BF344822, R86673, AW206720, AI961780, W79500, AI831018, AA514281, AA609867, T67539, W79599, F25102, AA807108, AI351521, F36686, BE164504, AA056972, BF917215, F24355, W16820, AA513661, F30483, AI349360, AI805040, AA532766, AW590360, AI962009, AI817647, BE140360, AI720757, BG236085, T64334, AI400242, AI832241, R86847, BF741663, AI383420, N74174, T65686, N92928, AA584402, AW138172, AA297326, BE170117, AA359080, AL515041, AL515035, AL513867, AL515375, AL040243, AL513907, AL514303, AI540832, BE905408, AI433976, BG179993, BF883916, BG260037, AV681987, AW274192, BG257535, BG036520, BF793644, AL135661, BE048026, BF525438, AV657079, AI475371, BF037097, BG031815, BE964812, BG108147, AV715263, AL121270, AI702406, AI687728, AI863014, AL513911, AI439087, BE887488, BF340104, AV755678, BF812933, AL046849, BE048071, AV655645, AW071417, AI440239, BG036846, AL514627, BE876033, BG032208, AI224992, AI250293, AI497733, BE904178, BE877769, AL513553, BE047952, AI433157, BF968041, AL513597, AI064830, BE018334, AV757705, AV705644, AI802542, BE881061, AI349772, AV681638, AV755581, AW071349, AI349933, BF344507, BE047863, AL045500, AI499393, AI758437, AI521012, BE781369, AL513803, AW195957, AI613017, AL036146, AI678302, AI568870, AI499463, AI249257, AW301409, AW103371, BF724691, AL513753, BG180996, AL514919, AI702433, AL513837, AV681630, AL047763, AV682252, AV758110, BF792469, AI866831, AI275175, BF969494, AI635461, AI498579, AI625079, AL036802, BF795712, AL515173, BE048135, BF791952, AW827203, AI538716, AL513693, AI285735, AW268253, BE785905, AW827249, AI564719, BE963035, BF971016, BG109270, AI620284, BE048081, BE964700, AI866608, BG168696, AV729334, AL119791, AV756560, BG252929, BG105099, BF968493, BE172767, AW117882, AV681951, BF726001, AV682249, BE777769, BG164371, AL513905, AV682266, AW238730, AL048871, AV682479, AV757455, AI800453, AI800433, BG058208, AV682264, AI934036, AI633419, AV757737, BE966388, AI866002, AI499131, AV681618, BG151247, AW169653, AW074993, AI612913, AI349645, AL121365, AV757853, AI349004, AV755613, AL514129, AW162071, BF970446, AF113615.1, AC040160.4, AK025992.1,</p>

					U23861.1, AF090901.1, AF090900.1, AF090934.1, AL157431.1, AL136892.1, AL442082.1, AL110221.1, BC008365.1, AL117457.1, AL136586.1, AL133075.1, AL136787.1, BC008387.1, AB056420.1, AB055303.1, S78214.1, BC007021.1, AL050393.1, AL389978.1, BC008488.1, AL050116.1, AL512733.1, AL080060.1, AF090903.1, AL442072.1, AL133640.1, BC008417.1, AF104032.1, AF078844.1, AL110196.1, AL390167.1, AL117460.1, AF125949.1, AL137527.1, AK026608.1, AL133016.1, BC003687.1, AL050149.1, AL162083.1, AF090943.1, AB048953.1, BC003683.1, AL049452.1, AF218014.1, AB049758.1, AL359596.1, AK026865.1, AJ242859.1, AL359601.1, AL133606.1, AB048964.1, AF111847.1, AK026784.1, AK026741.1, AB060916.1, AL050146.1, AK000212.1, AK025339.1, AL136749.1, AB056768.1, AL049938.1, AL136789.1, AB063046.1, AB055361.1, AF106862.1, AF090896.1, AB060887.1, AL050108.1, AB047615.1, AB063008.1, U42766.1, AK026045.1, AB056809.1, BC006807.1, AL122050.1, AB019565.1, AL133258.16, AB063070.1, AK025958.1, AB047801.1, BC001967.1, AL162006.1, AL136799.1, AK025084.1, AL133557.1, AL049466.1, AL049314.1, AL080137.1, AL359615.1, AK027868.1, AF219137.1, AL122093.1, AL136844.1, AL389982.1, AK026855.1, AL080124.1, AL512746.1, AL137283.1, AB060863.1, AB050510.1, AK026744.1, AL050277.1, AB060912.1, AL096744.1, AL133080.1, AL133093.1, AK025772.1, Y16645.1, AL137557.1, AB060908.1, AL122123.1, AL136768.1, AL050138.1, AL133565.1, AL122121.1, AK027096.1, AK026592.1, BC002733.1, AL137459.1, AF146568.1, AK026533.1, AK000618.1, AL359618.1, AF207829.1, BC008280.1, AL049382.1, AF125948.1, AK000137.1, AL353940.1, AK000083.1, AL512718.1, AL049430.1, AF271350.1, AL117394.1, AF091084.1, AK000445.1, AL137550.1, AL359941.1, AL512754.1, AK025092.1, AB062938.1, AK026452.1, X82434.1, U91329.1, AC007375.6, AK026583.1, BC008485.1, AL133344.28, AL110225.1, AB048954.1, AB060826.1, BC004556.1, AK000614.1, AF097996.1, BC006195.1, AL512719.1, AK025491.1, AK000652.1, AK026627.1, BC001045.1, AB055368.1, AB060825.1, AB051158.1, AF183393.1, AK026647.1, AB055315.1, AB060852.1, AK026542.1, AK026534.1, AK026480.1, AK024538.1, AL117435.1, AF225424.1, AL353745.7, AC026464.6, AB055366.1, AL117585.1, AB052191.1, AL117583.1, AB047904.1, BC002839.1, AL133560.1, AK026504.1, AK026959.1, AF177336.1, AP001346.1, AL512765.1, AC084881.19, AK026532.1, AK027113.1, AK000432.1, S61953.1, BC008983.1, AL136928.1, AB052200.1, AC009364.8, AL049464.1, AL158191.17, AL049300.1, AK000323.1, AK026353.1, AK026927.1, AC018643.3, AL050024.1, AL512883.5, AB056421.1, AK025414.1, AL512689.1, AP001666.1, AL512684.1, AB048974.1, BC007199.1, AL122110.1, BC008899.1, AL136845.1, AK025391.1, BC008070.1, AK026086.1, AK025967.1, AL353594.13, Z82022.1, BC004951.1, AK026528.1, AB049892.1, AK027204.1, AL353625.5, AK000718.1, AL355795.13, AL359583.1, AK027164.1, AL122098.1, AI889193.
HSYBG37	227	1056317	1 - 1224	15 - 1238	BE898532, BF034673, BF337228, BF528632, BE857436, BE732588, BF527968, BE888983, BG033426, AW372231, AA156935, BF915018, AV690944, AI140769, AW068552, AI818102, AI870885, AA135715, AA928421, AL047844, AI927908, AI762549, AL047845, AI797790, AI005050, AA917939,

HTADW91	228	844835	1 - 1467	15 - 1481	<p>AW873600, AI453114, AI420740, AW466885, AI432328, AI138677, AW188156, AW873561, BF980675, AW058508, BF770293, AA628898, AI094804, AI056500, BF820729, AI375863, BE857274, AW959629, AA905637, AI382011, AI860596, AA877674, AA513392, AI459017, W73121, AI242677, AI309547, BF819613, H16241, T70036, AA642494, AI675842, T03552, AI689235, BF919604, AI274910, AV748307, C00014, AI678921, AA993626, AI201747, AA742201, BF351125, BF770277, AW082362, BF914643, T30150, AI014513, R93245, H83130, AI538135, AI244946, AI952326, N45499, BF344569, AI685761, H05737, F20400, BF914807, AI094715, AI810996, AA320821, BF222389, H20376, H20185, H83129, T10108, AA370998, H12111, T70103, BF919644, AI800313, R47434, AI557606, AA299558, BF983106, BF347892, N47608, BF590090, AI141309, BF915129, AW385116, AA885897, BF917925, BF917920, N89795, AI797519, AA652696, AI193489, AA894705, T10109, AW189222, BF350004, BE829911, AI224610, AI423668, AA872954, AI207820, R39978, AI989675, AI439989, AI640906, BE046990, AI206927, AA136304, AW614497, AI751243, AA128437, AW772433, AI640184, AW385115, BF326281, W39052, AA595730, BF088390, AA731862, BF338332, BF111399, BF770143, BE767158, AA983866, AF302786.1, AE006467.1, AL031709.12, AK024842. 1.</p> <p>AL524277, AL525820, BE382621, BE906048, BE313348, BF311240, BF125870, BE314074, BE262971, BE261842, AW957565, AA434527, AI679032, AA429042, BF530443, AI269591, BF568093, AI751352, BF087452, AI926385, AW957563, AA427824, BF829853, BF207056, AI307680, AW751395, R73343, AA358983, AA985603, BF206540, BG029042, AA378137, AW016282, AA904900, BE767196, BE049123, AI538331, AI498177, AW084403, AW085619, AA428054, AW081391, AA461497, AW439261, AI081131, AI764997, BE672411, AW057677, AA761398, BE221467, AW080458, AI244183, AI634014, AW193005, AW339212, AW516122, AW027659, AW067803, AI954056, AW571944, AI633339, AA772395, AI916888, AI683203, AI422341, AW025425, BE671235, AI147736, AI090554, AI380245, AW439080, AI282915, BF196022, AA351024, AI565421, AI089315, BE501181, BF476178, AI205166, AW270733, AI751353, AA135896, AI936764, AW024598, AI767080, AI016528, AA135895, AV707105, AA620766, R10091, T49864, BF920348, T97167, AI831497, AA399634, AA152389, AA865196, AI277342, R50357, AW081268, BE503733, R11029, AA617807, R11077, AA649308, R10190, BF589988, R53497, N50819, R77618, AA568975, AA399595, AL525780, R72870, W68569, AA351025, R71797, AA912795, R79394, AW768731, BF903645, AA894462, H13235, H24510, BE811970, BF568932, H30448, AA627105, BF206286, BF340605, AW067872, BC008853.1, AL133581. 1.</p> <p>AW195720, AI765273, AI817356, AI928166, AI283845, BE503396, AW081502, BE349083, BF059350, AA419437, AA758800, AW206944, AA933673, AW104261, AI627565, AI264565, AW469909, AA845240, AA332515, AL021453. 1.</p>
HTAEE28	229	1018291	1 - 1327	15 - 1341	
HTDAF28	230	396835	1 - 898	15 - 912	<p>AI760170, AI150687, BF829200, AU158613, BF809865, AW273858, BE312404, BF316832, AU148518, BF314749, AU149720, BF315081, AI400198, AW062695, AI924082, BF314377, AW087415, BE047624, AI689214, AI684707, AA526748, BF315285, BE262228, AI566857, AI377786, AW167628, R65808, AA525309, R32753, AW663929, AI242434, BF206474, AI927229, R32754, AI956002,</p>



HTEEB42	232	206980	1 - 1008	15 - 1022	AI927230, AI701965, AU156607, BF349416, AW292033, AI368435, AA897436, BE314877, AI221593, AI612972, AI364630, BE185584, BF354201, AF352728.1, AF352729.1, AK022603. 1.
					AL522795, AA725566, AI421450, AL522796, AI199779, AA406389, AA912674, AW022835, AI952846, AI123727, BE218057, AW022646, N90730, BF846982, BF845761, AI652914, BF056970, AW020783, AI312805, AW393829, AI017553, AW393887, AW474261, AW264246, BF848293, AI366088, AI418268, T89217, AI052637, AW082343, BF221504, AW593293, AA865038, AI201753, BF091146, AI140139, AA987434, AA410345, BF846977, BF846980, AW900593, BF932982, BF932991, AW865421, AW136481, AI650503, AI432092, T89127, AA974715, AW261924, BE938414, AF255910.1, AY016009.1, AP001694.1, AP000087.1, AP000225.1, AP000226.1, AP000086.1, AP000223. 1.
HTEFU65	233	543396	1 - 1014	15 - 1028	AW072387, R83559, AI924465, AI364031, AW513660, BF361111, AA705541, AL162032. 1.
HTEGA76	234	381995	1 - 436	15 - 450	BF059486, AW293425, AI190540, AI201137, AI026778, AI016787, AA604883, AW172655, AA393061, AA709172, AC002456. 1.
HTELP17	236	836072	1 - 794	15 - 808	AW976593, AW275003, BF103848, AA744857, AI458735, AW013800, AA453589, AI684921, AI184517, AI376535, AA621297, AI970221, AW015543, AA969112, AA992291, AA442130, W01308, H72782, AL519628, AA129060, AA460996, AA721433, BF665557, BE170715, AA460649, BG035897, H72781, AI382100, BF541499, AW800324, AI806305, BF885871, AI868710, AI241242, BE386136, AV723953, R75918, N75771, AI865320, AI355277, AI500061, AW088944, AI491842, BE544111, AI866469, AW007955, AI800464, AI335426, AI348777, BE891834, BG179438, AW409772, AL037582, AL037602, AV758017, AV712838, AV713988, AI536563, H42557, AV713143, AV755673, AV702147, AI174799, BE881061, BF814357, BF797305, AV721644, AI345010, AW021717, BG029829, BF793891, BF909758, AI538817, AW827289, AL037454, AW025279, AA766104, AV717730, AI817523, AL046942, BG001293, BF969354, AI554818, BE887537, AI583032, AI473536, BE789373, AI582932, AI590043, AV714010, AV717397, BG121959, AV706915, AV706624, AW027374, AA744531, AV703585, BF924856, AI819545, BE883591, AW196078, AI811631, AL036705, AI929108, BF997967, AI345745, BF921291, BE964497, AI279925, AI873638, BG029053, AI923989, AI288152, AI305745, AI539800, BF816685, AI567582, AL040694, BF751288, BG166654, AL039276, AW090102, AI440238, AW161202, AI309306, AI401697, AI679959, AI345131, AL118781, AW078818, AI628325, AI697324, AI471429, T69241, AI470293, AI687568, BG033723, BF826429, AW965840, AA603709, AI371786, AI376748, AL043355, AI499986, BG032919, AI866770, BF924855, AW827211, AW059713, BG107590, AI125884, AI866465, BF092710, BE612681, AV750565, AI452707, AI446721, AI912438, AI288335, AI371243, AW020425, AI568138, AV682249, AV763927, AI972112, BG164558, BF811802, AW020397, AV713908, AW160905, AV681643, AW150826, AI864102, BG031447, AW193467, BG171892, AW162189, AI345415, AA514684, BE927769, AW059765, AL039274, AV648334, BF792047, BF970768, AI866780, AI570140, AI648663, AI363957, BF341210, BF792781, BG253033, AI890887, AL045626, BE957870, AI560679, AI434969, AL110306, AI561228, AA652505, AW172723, AI802244, AW022494, BE536058, AV705066, BF904265, AW410430, BF752997, AW183130, N81164,

				AI954293, AL120254, AW163464, BG112644, AW021662, AI571000, BG165979, AI927256, AI250852, AV682289, BF812963, AI336575, AL040241, AV682300, AI799364, AI445620, AL040449, AI656270, BF337602, BE965724, BF814412, BG260037, AA806719, AW264895, BE964614, BF904180, BF032768, AW151132, BE965432, AI474646, AW089664, AI653769, AW089275, AW020095, AI434656, Z99428, AW834325, AI923833, AI285419, BG122101, AC000772, AK026885.1, BC008365.1, AK024570.1, AB063093.1, Y14040.1, X82434.1, AL136748.1, AF078844.1, AF073483.1, AF285836.1, AL050092.1, AK025958.1, AK025414.1, AK025435.1, AL122118.1, BC003591.1, AF218006.1, AK026613.1, AF218023.1, BC007522.1, BC003410.1, BC007534.1, AF090901.1, AL133072.1, AL136882.1, AK026583.1, BC004310.1, AB062978.1, AK025407.1, AL389935.1, AL136884.1, AL512719.1, AL359596.1, AB056420.1, AF090903.1, AK026556.1, Z82022.1, AL110280.1, D83032.1, AB055805.1, AL137283.1, AB060826.1, AF262032.1, AL133049.1, AK026608.1, BC001328.1, AK027164.1, AL049283.1, AL122050.1, AK026522.1, AL137533.1, AL136864.1, S76508.1, AK024545.1, BC008785.1, BC002750.1, BC005890.1, AK024944.1, AL133665.1, AK025099.1, AF155827.1, BC008455.1, BC003120.1, BC003573.1, AL162008.1, BC001785.1, AK025906.1, BC006164.1, AF225424.1, AK025209.1, AK026762.1, BC001964.1, AL122100.1, AB056372.1, Y14314.1, AK026038.1, AK026534.1, AL133081.1, BC000316.1, AK026630.1, AK025410.1, AF252872.1, BC003122.1, BC005070.1, AL137479.1, BC006807.1, AL162002.1, AL080074.1, AK026784.1, AK027160.1, AB055303.1, AB060887.1, AL136766.1, AK026464.1, BC006408.1, BC006159.1, AL353802.14, AL117460.1, AL117649.1, AK026649.1, AF044323.1, S77771.1, AK024538.1, BC008196.1, AL133067.1, BC003683.1, BC008649.1, AK026528.1, BC008416.1, AB048913.1, AL049382.1, AK027173.1, AK026797.1, AK027146.1, AK000421.1, AB050431.1, AK025524.1, AL137488.1, U88966.1, BC002777.1, AK026462.1, BC002688.1, Y16645.1, AL050024.1, Y10936.1, AK026642.1, AK025084.1, AK000083.1, AB052191.1, AB055368.1, BC006525.1, AF081571.1, AK027111.1, S61953.1, AF090934.1, BC008387.1, AL136615.1, BC008284.1, AL136786.1, BC004530.1, AF110640.1, AF159615.1, AF106697.1, AB063079.1, AL512689.1, BC003590.1, AL157482.1, AL050393.1, AL136540.1, AK027113.1, BC004883.1, AK026480.1, AF177336.1, BC008723.1, AL136789.1, AL133062.1, U72621.3, BC004960.1, AB049849.1, AL136640.1, AB047623.1, AK024747.1, BC002409.1, AK025375.1, AF232009.1, AF217987.1, AK025092.1, AK025491.1, AL080162.1, BC003548.1, BC002473.1, AK000647.1, BC002844.1, AY033593.1, AL137480.1, AK026506.1, AL162004.1, AK024546.1, BC007499.1, BC005002.1, BC008673.1, AL512718.1, AB060897.1, AK027161.1, AF202636.1, BC000090.1, AF061795.1, AK026452.1, AF151685.1, AL136754.1, BC003684.1, AF260566.1, AK000391.1, AL353956.1, AL136586.1, BC005997.1, AL136784.1, AL133560.1, AK026408.1, BC007053.1, AK024588.1, AK027096.1, BC006091.1, AL357195.1, AF218014.1, AK025857.1, AB060879.1, AK026749.1, AK000257.1, BC007680.1, AL137558.1, AL583915.1, AL117432.1, AL389982.1, S78214.1, AK024992.1, AB051158.1, AL389939.1, BC003614.1, AJ299431.1, AK027082.1, BC002357.1, AF141289.1, AK026947.1, AB048954.1,

HTELS08	237	847090	1 - 1884	15 - 1898	AB048975.1, AL110221.1, AL096744.1, AB060914.1, AK026631.1, AK026542.1, BC007326.1, AB050407.1, AL136850.1, AB060893.1, AF132676.1, AB060873.1, AF061836.1, AL117583.1, AL137648.1, AL512733.1, AL390184.1, AL137711.1, AB060888.1, AL110158.1, AF090900.1, AF274348.1, AF036268.1, AF274347.1.
HTELS08	237	847090	1 - 1884	15 - 1898	AW664990, AA608835, BE972717, AA383680, AW572898, AI028204, AI554902, AI138881.
HTLEP53	238	634852	1 - 804	15 - 818	BF876683, AI755202, AI066646, AW613805, AA084609, AW769151, BE169870, AA601674, AI561210, BF926568, AW265614, BF826830, AI613389, AL042667, AL042670, AW130427, BF868994, AW471092, AV760019, AW576485, AI281818, AA225956, N64587, AU157209, BF941382, AI340151, AI859834, AW328202, AV754716, AW501278, BG222269, AI955029, AL134440, AI799569, BG250286, AW518030, AW576437, BF725884, BE396138, AW974363, T05118, AA524616, AI732682, AW268329, AI192440, AA669741, AW166920, D58782, AI653493, AW238341, BE301068, AI955718, BF923179, BF526964, AW438850, AW438662, U95742.1, AC019205.4, AC027125.4, AL356299.16, AC007216.2, AC008649.6, AC005484.2, AC005098.2, AC005740.1, AB020868.1, AC008569.6, AL359091.10, AL136527.9, AC005527.3, AC005000.2, AC005529.7, AL121809.6, AC090883.1, AC006312.8, AC004166.12, AF250325.1, AL008726.3, AL139396.17, AC010913.9, Z85987.13, AL590762.1, AL121658.2, AU246003.1, AP001781.4, AP001694.1, AC004867.5, AL13312.3, AL513550.9, AC008507.8, AL022476.2, AC005520.2, AC068533.7, AL160163.24, AC011485.6, AF111167.2, AC002544.1, AC004702.1, AL158141.14, AC005071.2, AC007191.1, AC005229.1, AL357515.26, AC010412.7, AL161670.4, AF196972.1, AL135927.14, AC007227.3, AC083884.6, AC004089.25, AL445483.13, AF165926.2, AC009060.7, AL359235.3, AC002350.1, AC005952.1, AC007052.4, AC020558.4, AL035071.17, AP000510.2, AC007731.14, AL121586.31, AL354815.10, AC005500.2, AC006014.2, AC005015.2, AL161893.24, AC005726.1, AC004985.2, AL161725.13, AC002390.1, AL450265.11, AL353135.32, AL160231.4, AC026672.44, AC004466.1, AC060231.6, AL360227.17, AL117382.28, AL021397.1, AC083863.2, AC011487.5, AL158824.11, AC018638.5, AL031283.26, AL121761.5, AC004242.1, AL020993.1, AL512641.9, AL121936.17, AC005280.3, AL035587.5, AC020916.7, AC067941.7, AC009812.17, AC012476.8, AL136228.8, AP001728.1, AL354808.24, AL049561.16, AL352984.4, AP000046.1, AC010378.6, AC000381.1, AC006480.3, AC006023.2, AL050308.9, AC005531.1, AL049776.3, AP000114.1, AC008551.5, AL031680.20, AL391827.18, AP001360.4, AL354707.17, AF111168.2, AL031683.2, U89337.1, AC010605.4, AL035367.5, AC002546.1, AL138724.12, AL033521.2, AC020906.6, AC078846.2, AC006452.4, AC007003.4, AC009244.24, AL049547.10, AL163279.2, AF064861.1, AC000025.2, AC027319.5, AL391280.15, AC008083.23, AC004253.1, AC008598.5, Y10196.1, AL049766.14, AL512666.6, AL138784.30, AC008891.7, AC004840.3, AC083873.3, AC005377.2, AC000360.35, AL049637.43, AL512378.7, AC008753.8, AC005488.2, AF001548.1, AC010422.7, AC009179.17, AC008623.4, AC004876.2, AP001717.1, AP001709.1, AC011465.4, AP000901.5, AL160471.5, AC006329.5, AL034405.16, AC008521.5, L44140.1, AC008481.7, U15177.1, AL162578.13,

					AC006449.19, Z97876.1, AC016830.5, AC008946.6, AL137792.11, AL109743.4, Z83844.5, AL049631.7, AC025275.4, AC091736.1, AP002453.3, AC006512.12, AC004491.1, AL356095.11, AC005291.1, AL136297.3, AC003982.1, AL022318.2, AC009086.5, AC005736.1, AC004824.3, Z84466.1, AP001670.1, AL157823.9, AC018904.6, AC002425.1, AF312032.1, AL109806.22, AL035413.19, AC006027.1, Z84469.1, AL513366.11, AC011737.10, AF196779.1, AC026756.15, AC008745.6, AC090527.3, AC006038.2, AC005318.1, AL391137.11, AC010543.8, AC005081.3, AC005522.2, AC005231.2, AC013726.7, AL109804.41, AC005399.19, AC004832.3, AC022148.5, AF134726.1, AC022007.3, AP002851.2, AL136084.11, AL031295.1, AP001748.1, AL121834.20, AC007686.5, AL049872.3, AL049569.13, AC016993.4, AC004805.1, AL133551.13, AL136966.27, AC004167.1, AP000237.1, AL117186.3, AL161747.5, AC005288.1, X54156.1, U94788.1, Z99127.1, AC016691.10, AC016025.12, AC010526.7, AC004890.2.
HTPCS72	240	854941	1 - 3421	15 - 3435	AV716024, BF032601, BE884480, BG107409, BE896847, AA534380, BF996760, BE935961, AA625472, BF593809, AI275974, AA758011, AI091865, AA770655, AA826573, AA642458, AA284480, AA308157, BF316735, AA150509, AI338707, H98214, AI085686, AI613457, AW007656, BE677803, BE092569, AW083271, BF890758, AA156713, BF315290, BF687549, AI079204, R38877, AI561066, AW629504, Z44870, AI638057, AA468549, BF445676, AW771735, BF852685, AW173317, BF882397, BE092420, AA368918, AW969242, AI254739, T80580, AA406249, F07793, R55262, R12721, BE832360, R55263, AW900776, BF357645, F05814, Z40638, F04054, AA321781, AW021358, AA714089, BF886411, BE149465, H91564, AA954780, BF871030, AI640665, BF036620, F02061, AA243079, BF307290, BF835491, BE774931, H90643, N44003, AA307326, AW135695, BE927559, AA242996, BF757045, AW999558, AI002239, BE567146, D19832, AW672798, BF089866, W73266, AF017388, BE932984, BE832354, BE707285, AB040946.1, AL008639.15, AF139898.1, AK027079.1, AF131746.1.
HTPIH83	241	919916	1 - 1467	15 - 1481	BE513091, BE304667, BG164062, AW385836, AW837727, AW837724, BF032123, BF541534, AW006504, AI769564, AW837723, AA552647, AW015998, AI343787, AI285131, AA976345, BE048787, AI949846, AI685788, AI953481, AW083920, BF819923, AI262767, AW194732, AA345449, AA639438, T86266, AI469683, AI244378, AI659323, T86158, BF758311, BG164241, AI932964, AV647382, BF104997, AI913916, AF177340.1, AL158821.16, AF250558.1.
HTSEW17	242	460579	1 - 638	15 - 652	AA779073, AI860913, AI028060, AI024955, BE549714, AW136463, R07163, AW612172, BF773051, AF007146.1, AF381980.1.
HTTBI76	243	637725	1 - 1697	15 - 1711	AA059411, BE568135, BE856883, BF435859, BF977217, AV701624, BE566398, BE856637, AA429722, BE564953, BE568948, BF214557, AA196423, AW237471, AA716665, AI377511, AA193289, N51319, BF248318, AI796263, AI770155, AA045194, BE380112, BF029088, AI185077, AA442760, BF214729, BE865742, AA810811, AI572127, AI494075, BE777718, AA128609, AA933879, BF027898, BF691014, BF977570, AV702879, AA421072, N63065, BE866018, AI373224, R99289, BG003427, BE568709, AA919169, AI580336, AW024454, BF057794, AA731146, AA128610, BF105164, AA062583, BF031391, BE866602, BF238619, AI758175, AA045378, D61992, BF211153,

					R99375, AA420992, AA194235, AA976350, AW135598, AI648675, BF436083, BE392607, AA383499, BF368270, AA878813, AA877180, BE379677, AI219249, AA846496, AV760348, AA380012, BE866426, AA453722, BF687711, BF213063, H86990, H86604, H86921, AL519369, AA383353, BE742087, AA007586, T85467, BE514581, BF573588, BF028113, AL521923, BF091941, BE548812, AI244008, H55168, AA379174, BE621508, AI200967, BF346162, AL137861.5, AC005690.8, AF271188. 1.
HTTBS64	244	1008159	1 - 2044	15 - 2058	AW801486, AL157701.2, AC006356.3, AC079033.12, AC025159.28, AL360078.16, AF002997.2, AL034428.4, AP001693.1, AL049873.3, Z83819.1, AL389889.11, AP001669.1, AL035552.9, AL590043.7, AC005406.2, AC009069.3, AC048346.13, AL354937.12, AL050401.5, AL136324.6, AL390800.4, AC073941.5, AP001597.1, AC012464.24, AC008277.4, AL121985.13, AC004988.2, AL359085.14, AC016623.5, AL163213.2, AL359850.7, AL357894.6, AL133247.1, AF003528.1, AC090946.1, AL021877.1, AL157779.6, AL137245.11, AC008250.23, AL031391.1, AL355530.6, AL589740.4, AL354750.12, AC002076.1, AL139090.11, AL354896.16, AC021863.5, AL121577.1, AL049732.11, AC012003.9, AL117259.6, AC010144.4, AC068061.5, AC068800.28, AL512452.7, AC010142.4, AC026691.4, AL354802.15, AL359252.17, AL512662.8, AC008506.7, AL022718.1, AC008462.6, AL356499.16, AL359332.2, AC019196.10, AL138479.4, AL137061.12, AP001331.1, AC019179.4, AL450333.13, AF003529.1, AL133444.4, AC034195.6, Z98753.1, AL161630.12, AL359273.11, AC005799.1, AL390247.11, AL392087.7, AL078594.36, AL139087.13, AL359999.11, AC004216.1, AC007543.4, AL033522.1, Z99571.1, AC012405.5, AL390959.12, AL160236.4, AL138773.4, AC079457.14, AC007158.10, AL359636.17, AC006979.2, AC002302.1, AL445687.5, AC005873.3, AC023095.7, AL136100.12, AC007214.13, AL162500.15, AC004160.1, AP001533.4, U82828.1, AC073273.9, AL034369.1, AL445985.10, AC006351.3, AC002065.1, AC022081.32, AL158053.14, AC010591.8, AC005284.1, AL355578.4, AC010534.7, AC005249.1, AC009466. 17.
HTWKE60	245	634083	1 - 393	15 - 407	BF664013, BF663121, BF663613, BF513422, AW450480, AW772007, AI741780, AA836248, AA927283, AI076561, AA832167, BE328468, AI122857, AA843388, AI051024, AA976372, AI128635, AI079659, AI377082, AI890194, BF433849, AI245546, BF431488, AA993068, W37347, AA664259, BF592129, AI078547, AI206154, BF476097, AA205973, AI628461, AA205959, AA564731, AW510675, AI333181, BE044542, AI220211, AA461495, AI205670, AW589962, AI659288, AI628811, AU145738, AI038255, AU146583, AI350952, N72913, AW172853, AA701323, AA879132, AA479117, AA928163, AI807914, AA053133, H96808, AI274742, AA446266, AW665166, AA983816, AI720197, BF593265, AI207274, F10245, R44951, W02663, AA773436, AI266048, BF438897, AA668420, AW593105, AA889759, H72321, AI051520, AA948635, AW973548, AA716356, AW418816, BE871115, AI677720, R07863, AI244578, AA206136, AA721247, AA626673, AA420708, R34711, R09438, AA653900, AI219624, T79760, AI269408, AA460570, BE743375, AI679772, W25733, AI927666, F30470, AA190369, AA420733, AA206135, AA206150, AK021823.1, AL021786. 1.
HTXAJ12	246	1310814	1 - 661	15 - 675	AA456896, BE783654, BG251027, AA768759, AI806785, AC083866.2, AC011005.7, V00584.1,

HTXJM03	247	603918	1 - 2384	15 - 2398	K01562.1, AL035087.20, U84680.1. AL518347, BE742019, AI114655, BF514929, AL118845, BF880731, AA236989, AI140989, AW813468, BE841331, AW582445, AA252594, AA618239, AI823453, AI280443, BF988837, AL042692, BF989072, HI5090, AW391644, BG011632, HI5570, Z43079, HI5630, AW813319, H22799, Z39170, AA252414, F07601, F11156, F05157, AA746494, HI5091, F08825, W68008, AW813329, F03848, F01404, AA804351, AC005829.1, AB033093.1, BC006271.1.
HTXKF95	248	891275	1 - 961	15 - 975	AI934965, AW574868, BF056901, BE676636, AA831751, AA814605, AW590381, AI857985, AA742405, BF592924, AI697328, BF059191, AW450001, AI341301, AI635420, AW610280, AA917582, AI418901, C01813, BE694168, AW291415, AA775165, BF798709, BF916068, AW975618, AW966330, AV718489, AW964468, AV699866, C14331, AV718681, AV720791, AW966065, AV718931, AW966389, AV724520, AW949645, D80522, AV738340, AV699550, D80133, D59610, AW973541, AV718692, D81026, AW960465, AW975613, AW975605, D80248, AW965177, AW377671, C14429, AW964532, AV722801, D80251, AW949641, AV720731, AW973488, AW973445, D51060, D51799, AW959469, AV741191, AV718938, AV718633, AW949630, C14389, AW978634, AW966062, D51423, AV720203, D80366, AW959799, AV719324, AW966059, AW973490, D59859, AV701004, AW959582, D80166, AW973474, AW964756, AW966053, D59619, D80269, AW978661, D80210, AW960553, D80240, D80253, AV719822, AW973307, AW964477, AW956434, AW973447, AV699927, AW966369, AV718707, AV720211, AV720878, AV719557, D80241, AV699447, D50979, AW966029, AW958993, D81030, AV723927, AW959136, AW966075, AW949656, D59373, AW949642, D80188, AW959202, AV720035, AW973334, AW966531, AW966534, D80227, AW966333, D58283, AW966022, D80212, AW978648, AW960473, D50995, AW966013, D59467, D51022, D80022, AW966041, D80219, AV719188, D80195, AW975621, AW959628, AW966378, AW973485, AW965163, D80391, D80164, D59275, AW966030, AW966054, AW966050, AW965158, D80043, D59787, AW959062, AV718440, AV719783, AV720028, D59502, AW959597, AW959570, AV719468, AV718800, AW965185, AW965197, AW965196, AW965184, AW965175, AV718844, AV720464, AV718770, AW973330, AW973482, AW958992, AW964488, AW962082, AW949654, D57483, C15076, D59889, D59927, D80196, AV720151, AV720533, D80024, D80378, AW949657, AA305409, AW966386, AW960454, AW962395, AW966368, AV720616, AW966032, AW966331, AW966398, AW966397, AV701839, AW956397, AW949629, AW949653, AW949631, AW949643, AW949618, AW949655, AV720220, AW966399, AA305578, AA514188, AV744662, D80038, AW966385, AW966043, AV744012, AW960504, AW973473, D80193, AW966388, AW962245, AW966380, AW965176, AW964737, AW966400, AW966332, AW960532, AV741187, AV741198, AV721386, AW949646, AW949633, AW949632, AW949658, D80045, C14014, AV744004, AA514186, AV744690, AV702035, D80268, AW752082, AV700889, AW753053, AW177440, AW966023, AV742001, AV720812, AV723097, AW966377, AW975623, D80439, AV744006, D59627, AW360811, AW178893, AV718530, BC008360.1, AC008083.23, AC004242.1, AF058696.1, AB028859.1, X67155.2, AF271371.1, D34614.1, AB002449.1, D88547.1, D50010.1, U79457.1, AB038216.1.

HTXON32	249	838288	1 - 1491	15 - 1505	AA746911, AA410788, AA704393, AA181917, BG222813, BE301584, AA683069, AA507822, AI056177, AA228778, AA084609, BE178231, BE178064, AI678867, AU147162, AV747362, AI857836, BF821968, AI754170, AW769654, AA825827, AA468975, AW513071, AW328202, AW069412, BF950533, AI962030, AI188049, BG250286, AI915075, BG222564, BG222326, AV733824, AV759632, AA584862, BE246405, AK000114.1, AL035088.1, AC003691.1, AP001359.4, AC004605.1, Z94056.1, AC010422.7, AC004125.1, AC012157.20, AC007912.6, AC005368.1, AL031257.1, AL354680.14, AC079353.5, AF130417.4, AC005011.2, AP001672.1, AC005255.1, AL445071.14, AL354977.10, AC006013.3, AP000851.4, AC008945.6, AC003689.1, AC002288.1, AC006211.1, AP002751.3, AL133391.5, Z98200.8, AF001905.1, AC006597.2, AC012450.9, AC005840.2, AC008699.5, AC007934.7, AC002422.1, AP000347.1, AL162831.5, AC009408.3, AC026191.3, AL136992.22, AC007436.1, AL590381.4, AC008840.4, AL008721.1, AC005841.3, AC021325.5, AL451061.8, AL117382.28, AC008511.6, AC004846.2, AL355365.10, AC004531.1, AC007652.1, AP001972.4, AP001727.1, AC087237.14, AC010465.7, AL157877.11, AL355984.11, AC010601.5, AL356095.11, AC004916.2, AC008264.10, AC025457.5, AP001561.4, AP000008.1, AC018719.4, AC007773.1, AC009094.7, AC010234.5, AC011890.4, AL355812.23, AC025471.5, AC020913.6, AP000704.2, AL135905.6, AC021863.5, AC022087.8, AC004659.1, AL022329.9, AC027342.4, AC019212.4, AC017100.4, AC020928.6, AC004104.1, AC019184.3, AL160274.9, AL161899.21, Z82194.1, AC026811.4, AC015842.9, AC002420.1, AL035079.14, AL390239.16, AC008012.8, AP001691.1, AL138819.9, AC009142.10, AL512449.6, AC024028.10, AC079408.25, AC005015.2, AL451126.18, AF011889.1, AL032821.2, AC004999.1, AF131216.1, AL109963.4, AL021939.1, AC008474.7, AC004089.25, AL391666.5, AL353135.32, AC005081.3, AF001551.1, AL096699.11, AC012312.8, AL031657.5, AL158832.13, AC006030.2, AL355336.15, AL050320.19, AC002553.1, AC005480.3, AF017104.1, AP001825.4, AC009779.18, AC016554.7, AC037433.6, AL033519.42, AC006313.1, AC019050.4, AL109623.9, AC012150.16, AL138749.13, AP000067.1, AL132994.4, AC004491.1, AC007993.15, AC025165.27, AF196970.1, AL157817.13, AC002377.1, AP000495.1, AB020869.1, AC009224.6, AC010582.6, AL160397.17, AL136040.5, AC068513.7, AL133173.19, AC004057.1, AC004616.1, AL353777.18, AP003473.2, AC008958.6, Z97635.10, AC073057.6, AC008427.7, AL137790.4, AC006316.2, AC005537.2, AC067941.7, AL035604.15, AC004021.1, AL035462.21, Z84480.1, AC003009.1, AC016778.3, AL355312.24, AC005746.1, AC005768.17, AC003690.1, Z97054.1, AP000577.4, AC069292.12, AL138696.16, AL354799.12, AL158828.14.
HUFCJ30	250	638402	1 - 854	15 - 868	AL533274, AI741266, AA194264, BF438670, BE855763, AI912191, BF109379, AI815187, AA521107, BE646628, AI911233, AA828445, AA429411, AI912933, AI423970, AI242299, BE042993, AW276617, AA905840, AA464614, AI394374, AW340805, AI096492, AI221797, AW129415, AI554269, AW969178, BG055418, AW029033, AW044596, AA582358, BE882568, AI870051, AA233165, AI933519, AI370473, BE676140, AW292630, AA429458, F03916, AA233241, F03174, AA193481,

					<p>H61820, AA193313, AW080606, AL533316, AA442046, AW975876, AW971403, AW974801, AW976024, AW975037, AW971975, AW972292, AW975965, AW975031, AW975002, AW971404, AW975019, AW975952, AW979127, AW974786, AW975105, AW975032, AW974964, AW979238, AW971968, AW975930, AW975954, AW969673, AW979090, AW975154, AW979002, AW969727, AW976023, AW975434, AW979204, AW969680, AW969643, AW974806, AW979098, AW975942, AW975971, AW973213, AW979176, AW973717, AW971326, AW974658, AW973219, AW969885, AW974338, AW971375, AW974998, AW975981, AW979208, AW970969, AW975149, AW979169, AW974975, AW975027, AW971732, AW970936, AW974802, AW974823, AW970942, AW975028, AW972377, AW973270, AW970010, AW972296, AW973185, AW975020, AW975632, AW969839, AW973750, AW973819, AW969816, AW976511, AW979294, AW979106, AW976031, AW975966, AW975058, AW975015, AW979212, AW976982, AW971378, AW976000, AW969852, AW979220, AW975585, AW979219, AW973209, AW974785, AW975692, AW972680, AW974101, AW973967, AW974971, AW972880, AW970962, AW972817, AW969861, AW973785, AW975025, AW975022, AW975649, AW973252, AW975959, AW973812, AW976506, AW979076, AW969637, AW972440, AW972154, AW971254, AW970889, AW979232, AW971305, AW979142, AW975230, AW973821, AW975899, AW972774, AW975167, AW972226, AW972660, AW973814, AW973775, AW973217, AW969768, AW975896, AW973779, AW976003, AW979054, AW975941, AW973211, AW969874, AW970113, AW972884, AW973189, AW973202, AW972695, AW973805, AW972719, AW976515, AW975976, AW979165, AW976510, AW971954, AW975975, AW969884, AW972943, AW969759, AW979083, BF592735, AW970587, AW973650, AW979175, AW969931, AW973986, AW979064, AW975938, AL359608. 1.</p>
HUVEB53	251	571200	1 - 1488	15 - 1502	<p>BE786669, AA453165, BG027754, AI694207, AW751021, BE140357, BE140309, BF673837, AI827679, AI597942, AI831626, BF572868, AW131344, AV726756, BE844218, BE162515, AA188243, AW188015, AW044629, AA877403, AI127993, BF691063, AA989288, AA453945, AA191206, AV748508, AA481849, AA405313, BF670519, AI167809, AA431686, AA846755, AI041097, AA305896, BE844200, BE844214, AI160824, HI13901, AA655009, R68945, W26226, AA861877, AW974213, HI1654, AW953548, AA453440, AI587514, AI076451, AA405350, H04206, AW751099, AA855040, AA974088, H43741, Z33442, AA825311, AA036965, AA188839, BE844205, H04207, AA923377, AA903946, AV693909, BE968480, AA761680, AV724398, AV724896, AA352991, AA330417, AA887483, D57665, N51756, AA206627, D61904, BF440004, AI248842, H58383, AA975213, D79380, AA205353, BE785631, AA344562, AA864363, D61991, BE467097, AA773771, AA649813, AW592162, AA642834, D79365, N47004, AW900901, AA036966, D61899, D58112, AA579902, AA865874, AA722600, R68832, R40852, H45338, BF131609, AA007516, H13852, AI828027, AA431480, BE149422, AV686924, AW074757, D20526, AB032988.1, AL021396. 8.</p>
HWAAD63	252	838626	1 - 3294	15 - 3308	<p>BG058664, AW953071, BF668217, AL046409, AI284640, AW406162, BF852604, AU123691, AL046205, AW303196, D82290, AW301350, AI334443, AV761286, AL121235, AW274349, AW600804, BF339640, BF677892, AV763892, BG032943, AI572924, AI801482, AI431303, AL044940,</p>



AV740801, AV764490, BG249643, AV762098, AI270117, AW969629, AI732378, AW265385, AI963720, AI708009, AI350211, AU147104, AW473163, AA669840, AV735495, AI149478, AV763971, AA581903, AV759518, AV760937, AI754955, AL041690, AI583283, AV710066, AV763550, BG236735, AU145314, AW502975, AV742057, BG167743, BF940837, AW193265, AV760777, BF914859, BF918590, AF074667, AV763122, BF918640, BE908796, BG036337, AW513362, AA491814, AV759362, BF725315, AV762050, AV763354, AW021583, BF919090, AI203955, AA531580, AA613232, AA490183, D82542, AW576391, AI623720, AV739452, AV728425, BE350475, AW500125, AA521323, AA665330, AV702857, AV730391, BF347791, AA610491, T40452, AA584167, AW474160, AI613280, AV762139, BE253048, AI192631, AI732865, AW020992, AA938105, AV733830, AF074677, AV652936, AW276817, BE872393, AW088846, AW438643, AI434695, AI345654, AW270270, AI610159, AW274346, AW265170, BF680041, BF854876, AA469451, AI589230, AA584145, AW833862, BE047069, AI570261, BF347740, AI619997, AW264934, AL042420, BF475381, AW518220, BF942454, AV762009, AI708125, BF697673, AW148792, BE297262, AW731867, AV759505, AA457542, BF991286, BF806176, AV728410, AU159337, AW089322, BE164494, AA774222, AI345518, AW963497, AV763255, AI696962, AL041706, F36273, AA496508, AV764228, AA478355, AV713243, AV761613, BE677379, BF736198, BF916517, AW079135, AV735370, R99597, AA652764, AW029038, AV725423, AA410828, AW169517, BG250302, AV761786, BE393367, BF872630, AF063563, AV764241, AA601294, BF827410, BF812839, AL119691, AV760378, AA177061, BG177715, BF674620, AI298710, AW169151, AA502104, AI345681, AI345675, AA633798, AV761925, AA682912, BF965007, AV733710, BF680074, AV762768, AA579362, BE139146, BF217299, AV762111, AV764578, AL118559.6, AB038653.1, AC020904.6, AC009497.3, AC006581.16, AF001549.1, AC004638.1, AC008267.6, AL121601.13, AL109865.36, AL356915.19, AC018809.4, AL163973.1, AC023908.6, AC011465.4, AL160237.4, AP000459.3, AC005081.3, AC044797.5, AC009154.5, AP001760.1, AL035367.5, AC007298.17, AL139350.17, AC006329.5, AC004019.20, AC006038.2, AC011455.6, AC008616.6, AL354932.26, AC011461.4, AL161892.9, AC005911.6, AC008265.15, U80017.1, AP003357.2, U91323.1, AC018636.4, AC005562.1, AL096701.14, AL080243.21, AC011450.4, AL133367.4, AL162458.10, AL354720.14, AC020658.6, AL158830.17, AL050318.13, AC005839.1, AP001687.1, AC009144.5, AC005041.2, Z99495.1, AC002565.1, AC022007.3, AC018769.2, AP000031.1, AC008372.6, AC011811.42, AC008688.7, AC009298.3, AP000047.1, AL445222.9, AL163248.2, AL139113.21, AC006435.7, AL136219.17, AC011495.6, AC008562.4, AC022308.17, AC008537.5, AP001667.1, AL133399.1, AL353135.32, AL121809.6, AC005696.1, AC073838.6, AC002476.1, AC006028.3, AP000115.1, AL445928.8, Z69666.1, AC005522.2, AC084783.2, AL133485.3, AC016025.12, AC004906.3, AC008649.6, AP000553.1, AC009470.4, AL031054.1, AC007193.1, AP000338.2, AL117334.29, AC009530.5, AP001346.1, AL034380.26, AC016830.5, AC008403.6, AL049550.5, AC027644.9, AC011930.5, AL109965.34, AC006241.1, AL049869.6, Z83844.5, Z98941.1, AL031283.26, AL159191.4,				
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					<p>AP000216.1, AC009996.7, AC015842.9, AL136295.3, AL139330.17, AC008745.6, AC005527.3, AC007731.14, U47924.1, AC012377.5, AC025212.5, AC005500.2, AC018751.30, Z93241.11, AL078638.9, AL354993.24, AC016769.10, AC005324.1, AL355517.12, AC074121.16, AC012170.6, AC006538.1, AP000962.2, AC004650.1, AC083884.6, AL354935.23, U52111.2, AC016027.15, AC079363.19, AP000113.1, AP000045.1, AL136123.19, AC007011.1, AL357150.7, AC008753.8, AL121675.36, AC002551.1, AL157838.24, AC009516.19, AC004865.1, AL139230.25, AC005529.7, AL050335.32, AC007216.2, AL049759.10, AP001716.1, AL021546.1, AC000360.35, AP001718.1, AE006639.1, AC025436.2, AL359091.10, AC004940.1, AC008101.15, AC003029.2, AL352978.6, AC020983.7, AL118520.26, AC007272.3, AC005154.1, AC078878.20, AL136980.5, AC005778.1, AC004971.3, AL033383.26, AC005921.3, AL159995.8, AC008068.4, AL008718.23, U95742.1, AC068712.6, AL024474.1, AC005031.1, AC017091.8, AC090514.1, AP001666.1, AL158040.13, AL161799.19, AL133387.8, AC003108.1, AC005808.1, AL109825.23, AC004033.3, Z98051.6, AC005295.1, AL353764.9, AC011236.8, AL132768.15, AC006285.11, Z99716.4, AL139396.17, AL096840.25, AL022098.1, AC005052.2, AC002300.1, AC007066.4, AL109797.18, AC004686.1, AL031662.26, AC008812.7, AL161656.20, AL136961.19, AC007404.4, AC020550.4, AJ003147.1, AP001858.4, AC021203.5, AC011559.3, AL117258.4, AC007620.30, AC010553.6, AP002028.1, AL356575.8, AP000299.1, AL121748.6, AL136300.22, AC016257.22, AC003684.1, AC004941.2, AL157406.19, AL049694.9, AL162853.17, U66059.1, AC026464.6, AL121972.17, AC013264.4, AL162426.20, AC006345.4, AC090960.1, AL049742.7, AC005037.2, AP000359.1, AC007051.3, AC018633.2, AL133174.15, AC008474.7, AC018635.6, AB023049.1, AC034198.6, AC022211.5.</p>
HWADJ89	253	799506	1 - 1755	15 - 1769	<p>AW958273, AW377130, AW574767, AW138853, BF111962, AA135712, AA156931, AW264402, AW117200, AI684896, AW339989, AA524553, AI394626, AI754796, AI860485, AI989549, AW129957, AI672796, BG056354, AA040909, AI000898, AI421190, AI693729, AW512733, AW044450, AI090274, AW205364, AW081734, BE939287, N35410, AA788655, N55117, AA844145, AI091868, N62863, AW302517, AI361489, AI628038, AA765992, AI800010, AI817849, BF800164, AI285397, AW403436, AA658416, AA648845, F13408, N73777, AA983941, R34886, AI024148, T04873, AA310563, Z33435, R72500, AI219780, AI149773, BG248348, R49268, BE305119, BE293618, AI743430, AW440724, T78828, BE249965, F10993, BE250024, AI371489, BE171979, N77769, AW235832, AI204426, R34492, N48042, BF899137, BF842700, R34372, Z38685, N99398, AI857456, AW841803, BE176205, AW899803, AA665233, AI290874, AW591407, AI432644, BF757092, AI623302, AW968355, AI431347, AI432653, AW081103, AI431230, AI431328, AI432654, AI432655, AI431310, AI431312, AI432650, AI432677, AW968356, BE672759, AI431353, AW971740, AW972091, AW972093, AW968729, AI431307, AI431316, AI432661, AI431354, AI431315, AI431337, AI431257, AI492519, BE672745, BE672732, AI791349, AI432666, AI432675, AW128900, BE672748, AI431238, AI492520, BE672719, AI432651, AI432647, AI431330, AI432674, AI432672, BF448552, AW972092, BE672767,</p>

					<p>AI431243, AI431248, AI432665, AI432657, AI432658, AI432649, BE672644, AI431255, BE672774, BE672742, AW969229, AI431254, BF589777, AI431350, AI431231, AI432662, AI431345, BE672738, AI431357, AW858522, AI431241, AI431351, AI431323, AI431346, AI431247, AI431318, AI432676, AI432673, AI431235, AI431321, AW128897, AI431340, AI432643, BE672792, AW128846, AI432664, AI431246, AW972090, AI432645, AW128884, BE672743, AI492510, BE672640, AL042931, AI431314, AW129223, AI431308, BE672749, BE672744, AI492509, BE672622, AI431751, BE672627, AL042729, AL045494, AL042655, BE672626, AL042523, AL042519, AL042853, AL031296.1, AK026719.1, AB007922.2, AF052104.1, AF064854.1, AL133082.1.</p>
HWBCP79	254	846382	1 - 1124	15 - 1138	<p>AW935696, BF358707, BF347791, BF674056, BE394054, BF945587, AA503600, BF347740, BF915002, AA169263, BF030530, AA580808, AA630672, AA127426, F12561, AV762741, AA828749, F34498, AV760634, BE005691, AA362349, BE790132, AA584876, AA838190, AI801482, BF149427, AI708009, BG059568, D52587, AA316905, M86120, AL121870.9, AL031255.1, AL135838.5, AC009533.9, AC002565.1, AE006462.1, Y18000.1, AC011895.4, AF312032.1, AC005529.7, AC006432.15, AC002094.1, AC005523.1, AP000350.1, AC007242.3, AC005087.2, AL163195.5, AC004882.2, AC018809.4, Z99716.4, Z83844.5, AL357075.17, AP000009.2, AP000150.1, AC006241.1, AC006251.3, AC007193.1, AC020893.5, U78027.1, AL031281.6, X76666.1, AL356983.33, AC005859.1, AC007272.3, AC007488.15, AC009570.13, AC007686.5, AL020997.1, AL499604.9, AP001965.2, AC005772.1, AL133153.3, AC005972.1, AC018637.3, AC021188.6, AC079177.21, AL445483.13, AL160414.18, AC008481.7, AC006597.2, AL136300.22, AC008753.8, AC010654.8, AC013726.7, AC007226.3, AL049870.3, AL157823.9, AC068724.7, U67825.1, AF111169.2, AC007318.4, AC004531.1, D26141.1, AC010489.4, AC007541.9, AL133405.17, Z98744.1, AP000111.1, AP000043.1, AL390074.17, AC010271.6, AC003690.1, AF241728.1, AL133418.4, AP001870.2, AC078878.20, AC004638.1, AL590762.1, AC005592.1, AL139809.16, AL136132.15, Z93023.1, AL009181.1, Z86090.10, AC005952.1, AC004953.1, AC005081.3, AC009086.5, AP001716.1, U47924.1, AC010422.7, AF283321.1, Z96074.4, AL117350.12, Z97192.2, AC020916.7, AC018821.4, AC011475.6, AL034451.26, U95090.1, AL590763.1, AC006120.1, AL356057.12, AC010126.3, AF114156.1, AL162390.9, AP003534.1, AL133243.1, AL162729.8, AL139054.1, AC003035.1, AB047869.1, AC005846.1, AL158052.10, AC009032.7, AC002455.1, Z83820.1, AC008891.7, AL163760.4, Z82182.2, AC007536.9, AC010519.6, AL138756.23, AC009475.4, AC005703.2, AC009779.18, AL358434.16, AL161629.10, AL391241.21, AC022212.4, AC008863.7.</p>
HWBEM18	255	949402	1 - 6715	15 - 6729	<p>BF970102, BF968719, BF982135, BE870739, BG177864, AW960084, AA502912, BE258859, BG248298, AI050870, AW006390, BE251201, AL119604, AW502481, BE536266, AW499634, AW401673, AI440347, AA310795, BG002481, AW501564, BE936524, AW501912, AW502940, AW501421, AW574552, AA524413, AW501492, AA524099, BF880552, BF313383, AV721883, BE675707, AW662450, AW970671, AW468042, AI688921, AW167025, AI970597, AI028774, AW188383, AW150222, AW083366, BE856306, AW504125, AA394112, AI802599, AA515127,</p>

					<p>AW499749, AW504539, BF974759, AA420978, AA632926, BE074737, BE074644, AW081261, BF755502, BE718644, BF892245, AW512533, BF932868, BF762091, BE840091, R82177, N55034, BF765799, AI814038, AW407844, AA504752, AA446015, AW748135, AA652891, AI000287, R82219, BE703532, F06324, BF814512, BF801697, BE551369, BF914193, AA478999, BF941470, BF765280, AV645387, AI191730, AA456551, AW406901, BF879805, BE703523, AW505537, AA577322, R11808, AA504654, BE718546, AA661852, BE913969, AA995856, AA321769, AI672210, AW270191, AA357086, AA477935, BE184342, BF879774, AA292315, BF364749, BF761813, BE831022, BE831018, BF154962, AL039259, BF360151, AW403756, BF763866, AA470467, AV755015, BF801703, BF907768, H62806, W76432, AA278264, H91643, BE184319, T99718, AW603140, BF843173, AA347047, BF901997, AA902263, BF448311, BF886674, AA278730, AW867470, BF800847, W04875, BF379714, BE831024, AI953093, AI200728, AA687290, AW511092, AI018458, AA486391, BF811403, W72039, BF767354, AW468272, AI675899, AI870318, BF968440, AI923553, AW027693, AB020713.1, AL117527.1, AK026042.1, AC090942.1, AC066589.3, AC069246.5, AC090885.1, AC027124.4, AC022234.3, AC090958.1, AC018841.3, X87546.1.</p>
HWBFX31	256	799427	1 - 1663	15 - 1677	H93613, N75773, N22551, AA884923, AW873751, H93612, AC039057. 8.
HWHGZ51	257	886212	1 - 1685	15 - 1699	<p>BE735965, AW372956, BF826018, BE735558, AW007721, AI955624, N30735, BF842481, AA531286, BE735650, AA476961, AA479609, AA709157, N29329, BF813297, AI680020, BF814081, W72299, AW450151, BF349121, AI342682, BE713111, AI207356, BE713103, BE713065, AA459897, AI206356, W23589, BF349122, BE939515, BE714549, W76325, W35267, AW272943, AA158001, AA442947, BE713172, BG012569, T69460, AA321599, AW135072, AA369339, BE713162, AI202455, AA369441, N57021, W68131, BE713086, BE713074, T69437, BE713165, AI301772, T70492, T70513, BF738317, AW389438, BE717812, D29356, BE717821, AA127911, AA846442, AA127966, BF842499, BF739402, BE140441, BE048026, AV658585, AL037582, AL037602, BG179993, AI802542, AV741327, AI628337, BE184331, N29277, AL040241, AW079572, BF812960, BF792961, AV743962, BG114432, AI469505, AL042745, AV757865, AL079963, BF970768, AI698391, BG110684, AI499285, BE968711, BF751302, AI570807, AI345416, AI345612, BF726183, AI824576, BF724420, AI345415, BE789764, F37323, AI627988, BG256090, AL043355, BG113188, BF856052, AV658845, AI884318, AI491775, AV656595, BF924855, AI886594, BG104927, AW051088, BF032768, BG111560, AV713305, BF526020, AI540458, AA287231, AW880037, AV733448, AI288285, AW983832, BF725534, BE047852, BG029086, BF970652, AA580663, BE963838, BG167986, AI538850, AI580436, AW673679, BF055899, AI440239, AI685005, AI687295, BG058150, AA833760, AA225339, AI241923, AI568138, BE018334, BG033723, BF054877, BG115626, BF338002, AL042744, AW303152, BG001235, AI673363, BG030364, AW090393, AI783997, AL042191, BF812938, BF752245, BF727091, AI670009, AV718258, AW020561, AI433157, AI818358, AI702073, AI473536, BF911521, AV757052, BF868489, AV682124, AI682798, T95813, BF812961, AI570966, AL036214, AI345778, AI932794, AW163834, BE879108, AW827206, AI564259, BG110682, BG058398, AA641818, AI633125, AI866040, BE535384, AI538564, AI638798, AW161156, AI915291, AW152182, BG117375, AW051059, BF811804, AV681993,</p>

					BG166654, AI866770, AL041150, AW104141, AI800440, BE777904, BF086116, AI433590, BE069120, AA806720, BE778453, BG180605, AL036673, BG112456, AI969655, AV733734, AL514887, AW827103, BG028116, BE964614, AI539847, AI863191, AI254727, AL039086, AI445992, BF858081, AI345608, BG029667, AI345688, AW083573, AI572717, AL036631, BF816037, AI613038, AW834302, BF909758, AW026882, AL038445, AI868931, R36271, BF872365, BG110517, BG257547, BG164558, AI267454, AI581033, AI623941, AI568114, AW167918, AA743354, AV714798, AV757035, AW983829, BF794478, AJ223603.2, AF082889.1, AC018758.2, AL353940.1, BC006472.1, AF132676.1, AF061836.1, AL137533.1, AL137294.1, AB055352.1, AF262032.1, AL137271.1, AL137480.1, AF056191.1, AL117435.1, AL080154.1, X72889.1, AK024538.1, BC004370.1, AB047941.1, AL389935.1, AL117460.1, BC002473.1, AL136845.1, BC006103.1, AL389939.1, AB050431.1, Z82022.1, AL512733.1, BC003548.1, AL122093.1, AB052191.1, AK026762.1, AL110221.1, AL049430.1, AL359583.1, AF217982.1, AF146568.1, AL050155.1, AB062750.1, AL137476.1, AL137557.1, AB060873.1, BC001655.1, X65873.1, AL512718.1, AB055371.1, AL137463.1, AB056427.1, AK027144.1, BC008282.1, AL442082.1, AK026600.1, AL133606.1, AF285167.1, AL122050.1, AB050410.1, AK026642.1, BC004925.1, AK025414.1, AB060908.1, AK025435.1, BC007534.1, AL136864.1, AL137488.1, AL080148.1, AL512719.1, AL512750.1, AK026480.1, BC003614.1, AL390154.1, BC004530.1, AB056421.1, BC007053.1, AK026593.1, AK024594.1, X82434.1, AK000418.1, AB047904.1, AB060929.1, AK027146.1, AL133665.1, AF104032.1, BC005007.1, BC008673.1, AB060826.1, AK026583.1, BC009395.1, AL359596.1, AB049758.1, AL137658.1, AL080137.1, AF100781.1, AF090934.1, AF358829.1, AL137478.1, AB055370.1, BC004899.1, AK026613.1, BC000090.1, AK026506.1, BC002733.1, AF321617.1, AB062978.1, AL137479.1, S61953.1, BC005858.1, AF218031.1, AK026885.1, BC002523.1, BC000348.1, AF061795.1, AF151685.1, AY034001.1, AK026542.1, AF320073.1, AF026816.2, AK024992.1, AK027081.1, AJ299431.1, AK026626.1, BC008417.1, AL137550.1, AK025491.1, AL359601.1, AL117578.1, AL136893.1, AL359618.1, U80742.1, AF111112.1, BC008387.1, AK027096.1, AL133640.1, AF225424.1, AL137459.1, AF183393.1, BC004958.1, AB048975.1, AB063079.1, AB056809.1, AB052200.1, AK026927.1, AF061943.1, AL096744.1, AF090901.1, AF057300.1, AF057299.1, X98834.1, AL133067.1, Y16645.1, AL133558.1, AK026528.1, AB063070.1, AK027161.1, BC006440.1, AF177336.1, AL136844.1, AB056420.1, AL137538.1, AB063093.1, AK027164.1, AL136843.1, BC007567.1, AL133075.1, AK025312.1, AF125948.1, AL583915.1, AL157431.1, AK025484.1, BC008078.1, BC008893.1, AK025465.1, AL137548.1, AL137521.1, AL136784.1, AL050366.1, AK027868.1, AF230496.1, AK026855.1, AB060905.1, AB060837.1, AL096720.1, AK026462.1, AL136540.1, BC004349.1, X69819.1, BC004951.1, BC004362.1, BC009212.1, Y14314.1, AL050149.1, AL110225.1, AL122098.1, AL136892.1, AL389982.1, AL136805.1, AL050277.1, AK026504.1, AK025391.1, AK027121.1, AB048953.1, AC021325.5, AL512754.1, AB063074.1, AK026630.1, AL080234.1, AL162062.1, AL359620.1, AB063100.1, BC001844.1, AB055361.1, AK024570.1, BC008983.1, AL359941.1, AB060912.1,

					BC003683.1, AB060897.1, AF143723.1, BC005168.1, AK026744.1, AL117416.1, BC004195.1, AK026784.1, AL122100.1, AL122118.1, AB056768.1, AY033593.1, BC007499.1, AL110280.1, AL133560.1, AL080124.1, AK026647.1, BC009033.1, AK024588.1, AK026086.1, AL049283.1, BC008899.1, AB048919.1, AK026959.1, AK000647.1, AB048974.1, AL136792.1, Z37987.1, AL137529.1, BC007680.1, BC006525.1, BC001056.1, AL050116.1, BC003684.1, AL137558. 1.
HWTBK81	258	460568	1 - 623	15 - 637	T89795, AW769449, AA774621, AA954176, BF879355, H04799, BF879528, BE394321, R39277, T89429, R42299, AA873122, AC009238.4, AC008268.3, AC016683. 7.

#### **Description of Table 4**

Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1B.2, column 5. Column 1 provides the tissue/cell source identifier code disclosed in Table 1B.2, Column 5. Columns 2-5 provide a description of the tissue or cell source. Note that "Description" and "Tissue" sources (i.e. columns 2 and 3) having the prefix "a\_" indicates organs, tissues, or cells derived from "adult" sources. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease." The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

Table 4

<u>Code</u>	<u>Description</u>	<u>Tissue</u>	<u>Organ</u>	<u>Cell Line</u>	<u>Disease</u>	<u>Vector</u>
AR022	a Heart	a Heart				
AR023	a Liver	a Liver				
AR024	a mammary gland	a mammary gland				
AR025	a Prostate	a Prostate				
AR026	a small intestine	a small intestine				
AR027	a Stomach	a Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				



AR054	Donor II Resting B Cells	Donor II Resting B Cells					
AR055	Heart	Heart					
AR056	Human Lung (clonotech)	Human Lung (clonotech)					
AR057	Human Mammary (clonotech)	Human Mammary (clonotech)					
AR058	Human Thymus (clonotech)	Human Thymus (clonotech)					
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)					
AR060	Kidney	Kidney					
AR061	Liver	Liver					
AR062	Liver (Clonotech)	Liver (Clonotech)					
AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic leukaemia					
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma					
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma					
AR066	normal breast	normal breast					
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)					
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045					
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208					
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005					
AR071	Ovarian Cancer	Ovarian Cancer					
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)					
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)					
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)					
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)					
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)					

AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)					
AR078	ovarian cancer 15799	ovarian cancer 15799					
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID					
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1					
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1					
AR082	ovarian cancer 94127303	ovarian cancer 94127303					
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304					
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029					
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045					
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001					
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC					
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd					
AR089	Prostate	Prostate					
AR090	Prostate (clonotech)	Prostate (clonotech)					
AR091	prostate cancer	prostate cancer					
AR092	prostate cancer #15176	prostate cancer #15176					
AR093	prostate cancer #15509	prostate cancer #15509					
AR094	prostate cancer #15673	prostate cancer #15673					
AR095	Small Intestine (Clonotech)	Small Intestine (Clonotech)					
AR096	Spleen	Spleen					
AR097	Thymus T cells activated	Thymus T cells activated					
AR098	Thymus T cells resting	Thymus T cells resting					
AR099	Tonsil	Tonsil					
AR100	Tonsil germinal center centroblast	Tonsil germinal center centroblast					
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell					

AR102	Tonsil lymph node	Tonsil lymph node					
AR103	Tonsil memory B cell	Tonsil memory B cell					
AR104	Whole Brain	Whole Brain					
AR105	Xenograft ES-2	Xenograft ES-2					
AR106	Xenograft SW626	Xenograft SW626					
AR119	001: IL-2	001: IL-2					
AR120	001: IL-2.1	001: IL-2.1					
AR121	001: IL-2 b	001: IL-2 b					
AR124	002 : Monocytes untreated (1hr)	002 : Monocytes untreated (1hr)					
AR125	002 : Monocytes untreated (5hrs)	002 : Monocytes untreated (5hrs)					
AR126	002: Control.1C	002: Control.1C					
AR127	002: IL2.1C	002: IL2.1C					
AR130	003 : Placebo-treated Rat Lacrimal Gland	003 : Placebo-treated Rat Lacrimal Gland					
AR131	003 : Placebo-treated Rat Submandibular Gland	003 : Placebo-treated Rat Submandibular Gland					
AR135	004 : Monocytes untreated (5hrs)	004 : Monocytes untreated (5hrs)					
AR136	004 : Monocytes untreated 1hr	004 : Monocytes untreated 1hr					
AR139	005: Placebo (48hrs)	005: Placebo (48hrs)					
AR140	006: pC4 (24hrs)	006: pC4 (24hrs)					
AR141	006: pC4 (48hrs)	006: pC4 (48hrs)					
AR152	007: PHA(1hr)	007: PHA(1hr)					
AR153	007: PHA(6HRS)	007: PHA(6HRS)					
AR154	007: PMA(6hrs)	007: PMA(6hrs)					
AR155	008: 1449 #2	008: 1449 #2					
AR161	01: A - max 24	01: A - max 24					
AR162	01: A - max 26	01: A - max 26					
AR163	01: A - max 30	01: A - max 30					

AR164	01: B - max 24	01: B - max 24					
AR165	01: B - max 26	01: B - max 26					
AR166	01: B - max 30	01: B - max 30					
AR167	1449 Sample	1449 Sample					
AR168	3T3P10 1.0uM insulin	3T3P10 1.0uM insulin					
AR169	3T3P10 10nM Insulin	3T3P10 10nM Insulin					
AR170	3T3P10 10uM insulin	3T3P10 10uM insulin					
AR171	3T3P10 No Insulin	3T3P10 No Insulin					
AR172	3T3P4	3T3P4					
AR173	Adipose (41892)	Adipose (41892)					
AR174	Adipose Diabetic (41611)	Adipose Diabetic (41611)					
AR175	Adipose Diabetic (41661)	Adipose Diabetic (41661)					
AR176	Adipose Diabetic (41689)	Adipose Diabetic (41689)					
AR177	Adipose Diabetic (41706)	Adipose Diabetic (41706)					
AR178	Adipose Diabetic (42352)	Adipose Diabetic (42352)					
AR179	Adipose Diabetic (42366)	Adipose Diabetic (42366)					
AR180	Adipose Diabetic (42452)	Adipose Diabetic (42452)					
AR181	Adipose Diabetic (42491)	Adipose Diabetic (42491)					
AR182	Adipose Normal (41843)	Adipose Normal (41843)					
AR183	Adipose Normal (41893)	Adipose Normal (41893)					
AR184	Adipose Normal (42452)	Adipose Normal (42452)					
AR185	Adrenal Gland	Adrenal Gland					
AR186	Adrenal Gland + Whole Brain	Adrenal Gland + Whole Brain					
AR187	B7(1hr)+ (inverted)	B7(1hr)+ (inverted)					
AR188	Breast (18275A2B)	Breast (18275A2B)					
AR189	Breast (4004199)	Breast (4004199)					
AR190	Breast (4004399)	Breast (4004399)					
AR191	Breast (4004943B7)	Breast (4004943B7)					
AR192	Breast (4005570B1)	Breast (4005570B1)					
AR193	Breast Cancer (4004127A30)	Breast Cancer (4004127A30)					

AR194	Breast Cancer (400443A21)	Breast Cancer (400443A21)							
AR195	Breast Cancer (4004643A2)	Breast Cancer (4004643A2)							
AR196	Breast Cancer (4004710A7)	Breast Cancer (4004710A7)							
AR197	Breast Cancer (4004943A21)	Breast Cancer (4004943A21)							
AR198	Breast Cancer (400553A2)	Breast Cancer (400553A2)							
AR199	Breast Cancer (9805C046R)	Breast Cancer (9805C046R)							
AR200	Breast Cancer (9806C012R)	Breast Cancer (9806C012R)							
AR201	Breast Cancer (ODQ 45913)	Breast Cancer (ODQ 45913)							
AR202	Breast Cancer (ODQ45913)	Breast Cancer (ODQ45913)							
AR203	Breast Cancer (ODQ4591B)	Breast Cancer (ODQ4591B)							
AR204	Colon Cancer (15663)	Colon Cancer (15663)							
AR205	Colon Cancer (4005144A4)	Colon Cancer (4005144A4)							
AR206	Colon Cancer (4005413A4)	Colon Cancer (4005413A4)							
AR207	Colon Cancer (4005570B1)	Colon Cancer (4005570B1)							
AR208	Control RNA #1	Control RNA #1							
AR209	Control RNA #2	Control RNA #2							
AR210	Cultured Preadipocyte (blue)	Cultured Preadipocyte (blue)							
AR211	Cultured Preadipocyte (Red)	Cultured Preadipocyte (Red)							
AR212	Donor II B-Cells 24hrs	Donor II B-Cells 24hrs							
AR213	Donor II Resting B-Cells	Donor II Resting B-Cells							

AR214	H114EP12 10nM Insulin	H114EP12 10nM Insulin					
AR215	H114EP12 (10nM insulin)	H114EP12 (10nM insulin)					
AR216	H114EP12 (2.6ug/ul)	H114EP12 (2.6ug/ul)					
AR217	H114EP12 (3.6ug/ul)	H114EP12 (3.6ug/ul)					
AR218	HUVEC #1	HUVEC #1					
AR219	HUVEC #2	HUVEC #2					
AR221	L6 undiff.	L6 undiff.					
AR222	L6 Undifferentiated	L6 Undifferentiated					
AR223	L6P8 + 10nM Insulin	L6P8 + 10nM Insulin					
AR224	L6P8 + HS	L6P8 + HS					
AR225	L6P8 10nM Insulin	L6P8 10nM Insulin					
AR226	Liver (00-06-A007B)	Liver (00-06-A007B)					
AR227	Liver (96-02-A075)	Liver (96-02-A075)					
AR228	Liver (96-03-A144)	Liver (96-03-A144)					
AR229	Liver (96-04-A138)	Liver (96-04-A138)					
AR230	Liver (97-10-A074B)	Liver (97-10-A074B)					
AR231	Liver (98-09-A242A)	Liver (98-09-A242A)					
AR232	Liver Diabetic (1042)	Liver Diabetic (1042)					
AR233	Liver Diabetic (41616)	Liver Diabetic (41616)					
AR234	Liver Diabetic (41955)	Liver Diabetic (41955)					
AR235	Liver Diabetic (42352R)	Liver Diabetic (42352R)					
AR236	Liver Diabetic (42366)	Liver Diabetic (42366)					
AR237	Liver Diabetic (42483)	Liver Diabetic (42483)					
AR238	Liver Diabetic (42491)	Liver Diabetic (42491)					
AR239	Liver Diabetic (99-09-A281A)	Liver Diabetic (99-09-A281A)					
AR240	Lung	Lung					
AR241	Lung (27270)	Lung (27270)					
AR242	Lung (2727Q)	Lung (2727Q)					
AR243	Lung Cancer (4005116A1)	Lung Cancer (4005116A1)					
AR244	Lung Cancer (4005121A5)	Lung Cancer (4005121A5)					
AR245	Lung Cancer	Lung Cancer (4005121A5))					







	(42395)	(42395)							
AR295	Skeletal Muscle Diabetic (42483)	Skeletal Muscle Diabetic (42483)							
AR296	Skeletal Muscle Diabetic (42491)	Skeletal Muscle Diabetic (42491)							
AR297	Skeletal Muscle Diabetic 42352	Skeletal Muscle Diabetic 42352							
AR298	Skeletal Muscle (42461)	Skeletal Muscle (42461)							
AR299	Small Intestine	Small Intestine							
AR300	Stomach	Stomach							
AR301	T-Cell + HDPBQ71.fc 1449 16hrs	T-Cell + HDPBQ71.fc 1449 16hrs							
AR302	T-Cell + HDPBQ71.fc 1449 6hrs	T-Cell + HDPBQ71.fc 1449 6hrs							
AR303	T-Cell + IL2 16hrs	T-Cell + IL2 16hrs							
AR304	T-Cell + IL2 6hrs	T-Cell + IL2 6hrs							
AR306	T-Cell Untreated 16hrs	T-Cell Untreated 16hrs							
AR307	T-Cell Untreated 6hrs	T-Cell Untreated 6hrs							
AR308	T-Cells 24 hours	T-Cells 24 hours							
AR309	T-Cells 24 hrs	T-Cells 24 hrs							
AR310	T-Cells 24 hrs.	T-Cells 24 hrs.							
AR311	T-Cells 24hrs	T-Cells 24hrs							
AR312	T-Cells 4 days	T-Cells 4 days							
AR313	Thymus	Thymus							
AR314	TRE	TRE							
AR315	TREC	TREC							
AR317	B lymphocyte, (non-T; non-B)	B lymphocyte, (non-T; non-B)							
AR318	001 - 293 RNA (Vector Control)	001 - 293 RNA (Vector Control)							
AR326	001 - 293 RNA (Vector Control)	001 - 293 RNA (Vector Control)							
AR327	001: Control	001: Control							
AR328	001: Control.1	001: Control.1							

AR355	Acute Lymphocyte Leukemia	Acute Lymphocyte Leukemia					
AR356	AML Patient #11	AML Patient #11					
AR357	AML Patient #2	AML Patient #2					
AR358	AML Patient #2 SGAH	AML Patient #2 SGAH					
AR359	AML Patient#2	AML Patient#2					
AR360	Aorta	Aorta					
AR361	B Cell	B Cell					
AR362	B lymphoblast	B lymphoblast					
AR363	B lymphocyte	B lymphocyte					
AR364	B lymphocytes	B lymphocytes					
AR365	B-cell	B-cell					
AR366	B-Cells	B-Cells					
AR367	B-Lymphoblast	B-Lymphoblast					
AR368	B-Lymphocytes	B-Lymphocytes					
AR369	Bladder	Bladder					
AR370	Bone Marrow	Bone Marrow					
AR371	Bronchial Epithelial Cell	Bronchial Epithelial Cell					
AR372	Bronchial Epithelial Cells	Bronchial Epithelial Cells					
AR373	Caco-2A	Caco-2A					
AR374	Caco-2B	Caco-2B					
AR375	Caco-2C	Caco-2C					
AR376	Cardiac #1	Cardiac #1					
AR377	Cardiac #2	Cardiac #2					
AR378	Chest Muscle	Chest Muscle					
AR381	Dendritic Cell	Dendritic Cell					
AR382	Dendritic cells	Dendritic cells					
AR383	E.coli	E.coli					
AR384	Epithelial Cells	Epithelial Cells					
AR385	Esophagus	Esophagus					
AR386	FPPS	FPPS					
AR387	FPPSC	FPPSC					



AR416	NK	NK							
AR417	NK cell	NK cell							
AR418	NK cells	NK cells							
AR419	NKYa	NKYa							
AR420	NKYa019	NKYa019							
AR421	Ovary	Ovary							
AR422	Patient #11	Patient #11							
AR423	Peripheral blood	Peripheral blood							
AR424	Primary Adipocytes	Primary Adipocytes							
AR425	Promyeloblast	Promyeloblast							
AR427	RSSWT	RSSWT							
AR428	RSSWTC	RSSWTC							
AR429	SW 480(G1)	SW 480(G1)							
AR430	SW 480(G2)	SW 480(G2)							
AR431	SW 480(G3)	SW 480(G3)							
AR432	SW 480(G4)	SW 480(G4)							
AR433	SW 480(G5)	SW 480(G5)							
AR434	T Lymphoblast	T Lymphoblast							
AR435	T Lymphocyte	T Lymphocyte							
AR436	T-Cell	T-Cell							
AR438	T-Cell,	T-Cell,							
AR439	T-Cells	T-Cells							
AR440	T-lymphoblast	T-lymphoblast							
AR441	Th 1	Th 1							
AR442	Th 2	Th 2							
AR443	Th1	Th1							
AR444	Th2	Th2							
H0004	Human Adult Spleen	Human Adult Spleen			Spleen				Uni-ZAP XR
H0007	Human Cerebellum	Human Cerebellum			Brain				Uni-ZAP XR
H0008	Whole 6 Week Old Embryo								Uni-ZAP XR
H0009	Human Fetal Brain								Uni-ZAP XR

H0012	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0013	Human 8 Week Whole Embryo	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0014	Human Gall Bladder	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0015	Human Gall Bladder, fraction II	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0016	Human Greater Omentum	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0017	Human Greater Omentum	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0022	Jurkat Cells	Jurkat T-Cell Line				Lambda ZAP II
H0024	Human Fetal Lung III	Human Fetal Lung	Lung			Uni-ZAP XR
H0025	Human Adult Lymph Node	Human Adult Lymph Node	Lymph Node			Lambda ZAP II
H0030	Human Placenta					Uni-ZAP XR
H0031	Human Placenta	Human Placenta	Placenta			Uni-ZAP XR
H0032	Human Prostate	Human Prostate	Prostate			Uni-ZAP XR
H0033	Human Pituitary	Human Pituitary				Uni-ZAP XR
H0036	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0038	Human Testes	Human Testes	Testis			Uni-ZAP XR
H0039	Human Pancreas Tumor	Human Pancreas Tumor	Pancreas	disease		Uni-ZAP XR
H0040	Human Testes Tumor	Human Testes Tumor	Testis	disease		Uni-ZAP XR
H0041	Human Fetal Bone	Human Fetal Bone	Bone			Uni-ZAP XR
H0042	Human Adult Pulmonary	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0046	Human Endometrial Tumor	Human Endometrial Tumor	Uterus	disease		Uni-ZAP XR
H0050	Human Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0051	Human Hippocampus	Human Hippocampus	Brain			Uni-ZAP XR
H0052	Human Cerebellum	Human Cerebellum	Brain			Uni-ZAP XR
H0056	Human Umbilical Vein, Endo. remake	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0057	Human Fetal Spleen					Uni-ZAP XR
H0059	Human Uterine Cancer	Human Uterine Cancer	Uterus	disease		Lambda ZAP II
H0063	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR
H0068	Human Skin Tumor	Human Skin Tumor	Skin	disease		Uni-ZAP XR

H0069	Human Activated T-Cells	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0070	Human Pancreas	Human Pancreas	Pancreas			Uni-ZAP XR
H0071	Human Infant Adrenal Gland	Human Infant Adrenal Gland	Adrenal gland			Uni-ZAP XR
H0073	Human Leiomyeloid Carcinoma	Human Leiomyeloid Carcinoma	Muscle		disease	Uni-ZAP XR
H0075	Human Activated T-Cells (II)	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0077	Human Thymus Tumor	Human Thymus Tumor	Thymus		disease	Lambda ZAP II
H0081	Human Fetal Epithelium (Skin)	Human Fetal Skin	Skin			Uni-ZAP XR
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Jurkat Cells				Uni-ZAP XR
H0085	Human Colon	Human Colon				Lambda ZAP II
H0086	Human epithelioid sarcoma	Epithelioid Sarcoma, muscle	Sk Muscle		disease	Uni-ZAP XR
H0087	Human Thymus	Human Thymus				pBluescript
H0090	Human T-Cell Lymphoma	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0096	Human Parotid Cancer	Human Parotid Cancer	Parotid		disease	Lambda ZAP II
H0098	Human Adult Liver, subtracted	Human Adult Liver	Liver			Uni-ZAP XR
H0100	Human Whole Six Week Old Embryo	Human Whole Six Week Old Embryo	Embryo			Uni-ZAP XR
H0102	Human Whole 6 Week Old Embryo (II), subt	Human Whole Six Week Old Embryo	Embryo			pBluescript
H0108	Human Adult Lymph Node, subtracted	Human Adult Lymph Node	Lymph Node			Uni-ZAP XR
H0111	Human Placenta, subtracted	Human Placenta	Placenta			pBluescript
H0112	Human Parathyroid Tumor, subtracted	Human Parathyroid Tumor	Parathyroid			pBluescript
H0122	Human Adult Skeletal Muscle	Human Skeletal Muscle	Sk Muscle			Uni-ZAP XR

H0123	Human Fetal Dura Mater	Human Fetal Dura Mater	Brain			Uni-ZAP XR
H0124	Human Rhabdomyosarcoma	Human Rhabdomyosarcoma	Sk Muscle		disease	Uni-ZAP XR
H0125	Cem cells cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0128	Jurkat cells, thiouridine activated	Jurkat Cells				Uni-ZAP XR
H0130	LNCAP untreated	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0131	LNCAP + 0.3nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0132	LNCAP + 30nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0134	Raji Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0135	Human Synovial Sarcoma	Human Synovial Sarcoma	Synovium			Uni-ZAP XR
H0136	Supt Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0139	Activated T-Cells, 4 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0140	Activated T-Cells, 8 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0141	Activated T-Cells, 12 hrs.	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0144	Nine Week Old Early Stage Human	9 Wk Old Early Stage Human	Embryo			Uni-ZAP XR
H0149	7 Week Old Early Stage Human, subtraced	Human Whole 7 Week Old Embryo	Embryo			Uni-ZAP XR
H0150	Human Epididymus	Epididymis	Testis			Uni-ZAP XR
H0151	Early Stage Human Liver	Human Fetal Liver	Liver			Uni-ZAP XR
H0156	Human Adrenal Gland Tumor	Human Adrenal Gland Tumor	Adrenal Gland		disease	Uni-ZAP XR
H0159	Activated T-Cells, 8 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0160	Activated T-Cells, 12 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0161	Activated T-Cells, 24 hrs., ligation 2	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0163	Human Synovium	Human Synovium	Synovium			Uni-ZAP XR

H0165	Human Prostate Cancer, Stage B2	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0166	Human Prostate Cancer, Stage B2 fraction	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0169	Human Prostate Cancer, Stage C fraction	Human Prostate Cancer, stage C	Prostate		disease	Uni-ZAP XR
H0170	12 Week Old Early Stage Human	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0171	12 Week Old Early Stage Human, II	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0172	Human Fetal Brain, random primed	Human Fetal Brain	Brain			Lambda ZAP II
H0176	CAMA1Ee Cell Line	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0177	CAMA1Ee Cell Line	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0178	Human Fetal Brain	Human Fetal Brain	Brain			Uni-ZAP XR
H0179	Human Neutrophil	Human Neutrophil	Blood	Cell Line		Uni-ZAP XR
H0180	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0181	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0182	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0187	Resting T-Cell	T-Cells	Blood	Cell Line		Lambda ZAP II
H0188	Human Normal Breast	Human Normal Breast	Breast			Uni-ZAP XR
H0192	Cem Cells, cyclohexamide treated, subtra	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0194	Human Cerebellum, subtracted	Human Cerebellum	Brain			pBluescript
H0196	Human Cardiomyopathy, subtracted	Human Cardiomyopathy	Heart			Uni-ZAP XR
H0204	Human Colon Cancer, subtracted	Human Colon Cancer	Colon			pBluescript
H0208	Early Stage Human Lung,	Human Fetal Lung	Lung			pBluescript



	subtracted						
H0211	Human Prostate, differential expression	Human Prostate	Prostate				pBluescript
H0212	Human Prostate, subtracted	Human Prostate	Prostate				pBluescript
H0213	Human Pituitary, subtracted	Human Pituitary					Uni-ZAP XR
H0214	Raji cells, cyclohexamide treated, subtracted	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line			pBluescript
H0216	Supt cells, cyclohexamide treated, subtracted	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line			pBluescript
H0218	Activated T-Cells, 0hrs, subtracted	Activated T-Cells	Blood	Cell Line			Uni-ZAP XR
H0220	Activated T-Cells, 4 hrs, subtracted	Activated T-Cells	Blood	Cell Line			Uni-ZAP XR
H0224	Activated T-Cells, 12 hrs, subtracted	Activated T-Cells	Blood	Cell Line			Uni-ZAP XR
H0225	Activated T-Cells, 12hrs, differentially expressed	Activated T-Cells	Blood	Cell Line			Uni-ZAP XR
H0231	Human Colon, subtraction	Human Colon					pBluescript
H0233	Human Fetal Heart, Differential (Adult-Specific)	Human Fetal Heart	Heart				pBluescript
H0235	Human colon cancer, metastaticized to liver, subtraction	Human Colon Cancer, metastaticized to liver	Liver				pBluescript
H0239	Human Kidney Tumor	Human Kidney Tumor	Kidney			disease	Uni-ZAP XR
H0240	C7MCF7 cell line, estrogen treated, Differential	C7MCF7 Cell Line, estrogen treated	Breast	Cell Line			Uni-ZAP XR
H0242	Human Fetal Heart, Differential (Fetal-Specific)	Human Fetal Heart	Heart				pBluescript
H0244	Human 8 Week Whole Embryo, subtracted	Human 8 Week Old Embryo	Embryo				Uni-ZAP XR

H0250	Human Activated Monocytes	Human Monocytes					Uni-ZAP XR
H0251	Human Chondrosarcoma	Human Chondrosarcoma	Cartilage			disease	Uni-ZAP XR
H0252	Human Osteosarcoma	Human Osteosarcoma	Bone			disease	Uni-ZAP XR
H0253	Human adult testis, large inserts	Human Adult Testis	Testis				Uni-ZAP XR
H0254	Breast Lymph node cDNA library	Breast Lymph Node	Lymph Node				Uni-ZAP XR
H0255	breast lymph node CDNA library	Breast Lymph Node	Lymph Node				Lambda ZAP II
H0256	HL-60, unstimulated	Human HL-60 Cells, unstimulated	Blood		Cell Line		Uni-ZAP XR
H0257	HL-60, PMA 4H	HL-60 Cells, PMA stimulated 4H	Blood		Cell Line		Uni-ZAP XR
H0261	H. cerebellum, Enzyme subtracted	Human Cerebellum	Brain				Uni-ZAP XR
H0263	human colon cancer	Human Colon Cancer	Colon			disease	Lambda ZAP II
H0264	human tonsils	Human Tonsil	Tonsil				Uni-ZAP XR
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco	T-Cells	Blood		Cell Line		Uni-ZAP XR
H0266	Human Microvascular Endothelial Cells, fract. A	HMEC	Vein		Cell Line		Lambda ZAP II
H0267	Human Microvascular Endothelial Cells, fract. B	HMEC	Vein		Cell Line		Lambda ZAP II
H0268	Human Umbilical Vein Endothelial Cells, fract. A	HUVE Cells	Umbilical vein		Cell Line		Lambda ZAP II
H0269	Human Umbilical Vein Endothelial Cells, fract. B	HUVE Cells	Umbilical vein		Cell Line		Lambda ZAP II
H0270	HPAS (human pancreas, subtracted)	Human Pancreas	Pancreas				Uni-ZAP XR
H0271	Human Neutrophil, Activated	Human Neutrophil - Activated	Blood		Cell Line		Uni-ZAP XR

H0272	HUMAN TONSILS, FRACTION 2	Human Tonsil	Tonsil			Uni-ZAP XR
H0274	Human Adult Spleen, fractionII	Human Adult Spleen	Spleen			Uni-ZAP XR
H0275	Human Infant Adrenal Gland, Subtracted	Human Infant Adrenal Gland	Adrenal gland			pBluescript
H0280	K562 + PMA (36 hrs)	K562 Cell line	cell line	Cell Line		ZAP Express
H0284	Human OB MG63 control fraction I	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0286	Human OB MG63 treated (10 nM E2) fraction I	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0288	Human OB HOS control fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0290	Human OB HOS treated (1 nM E2) fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0292	Human OB HOS treated (10 nM E2) fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0294	Amniotic Cells - TNF induced	Amniotic Cells - TNF induced	Placenta	Cell Line		Uni-ZAP XR
H0295	Amniotic Cells - Primary Culture	Amniotic Cells - Primary Culture	Placenta	Cell Line		Uni-ZAP XR
H0298	HCBB's differential consolidation	CAMA1Ee Cell Line	Breast	Cell Line		Uni-ZAP XR
H0300	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0305	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0306	CD34 depleted Buffy Coat (Cord Blood)	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0309	Human Chronic Synovitis	Synovium, Chronic Synovitis/ Osteoarthritis	Synovium		disease	Uni-ZAP XR
H0310	human caudate nucleus	Brain	Brain			Uni-ZAP XR
H0313	human pleural cancer	pleural cancer			disease	pBluescript

H0316	HUMAN STOMACH	Human Stomach	Stomach				Uni-ZAP XR
H0318	HUMAN B CELL LYMPHOMA	Human B Cell Lymphoma	Lymph Node		disease		Uni-ZAP XR
H0320	Human frontal cortex	Human Frontal Cortex	Brain				Uni-ZAP XR
H0327	human corpus colosum	Human Corpus Callosum	Brain				Uni-ZAP XR
H0328	human ovarian cancer	Ovarian Cancer	Ovary		disease		Uni-ZAP XR
H0329	Dermatofibrosarcoma Protuberance	Dermatofibrosarcoma Protuberans	Skin		disease		Uni-ZAP XR
H0331	Hepatocellular Tumor	Hepatocellular Tumor	Liver		disease		Lambda ZAP II
H0333	Hemangiopericytoma	Hemangiopericytoma	Blood vessel		disease		Lambda ZAP II
H0334	Kidney cancer	Kidney Cancer	Kidney		disease		Uni-ZAP XR
H0341	Bone Marrow Cell Line (RS4;11)	Bone Marrow Cell Line RS4;11	Bone Marrow	Cell Line			Uni-ZAP XR
H0343	stomach cancer (human)	Stomach Cancer - 5383A (human)			disease		Uni-ZAP XR
H0346	Brain-medulloblastoma	Brain (Medulloblastoma)-9405C006R	Brain		disease		Uni-ZAP XR
H0350	Human Fetal Liver, mixed 10 & 14 week	Human Fetal Liver, mixed 10&14 Week	Liver				Uni-ZAP XR
H0351	Glioblastoma	Glioblastoma	Brain		disease		Uni-ZAP XR
H0352	wilm's tumor	Wilm's Tumor			disease		Uni-ZAP XR
H0354	Human Leukocytes	Human Leukocytes	Blood	Cell Line			pCMVSPORT 1
H0355	Human Liver	Human Liver, normal Adult					pCMVSPORT 1
H0356	Human Kidney	Human Kidney	Kidney				pCMVSPORT 1
H0357	H. Normalized Fetal Liver, II	Human Fetal Liver	Liver				Uni-ZAP XR
H0359	KMH2 cell line	KMH2					ZAP Express
H0369	H. Atrophic Endometrium	Atrophic Endometrium and myometrium					Uni-ZAP XR
H0370	H. Lymph node breast Cancer	Lymph node with Met. Breast Cancer			disease		Uni-ZAP XR
H0373	Human Heart	Human Adult Heart	Heart				pCMVSPORT 1
H0375	Human Lung	Human Lung					pCMVSPORT 1

H0379	Human Tongue, frac 1	Human Tongue				pSport I
H0380	Human Tongue, frac 2	Human Tongue				pSport I
H0381	Bone Cancer	Bone Cancer			disease	Uni-ZAP XR
H0383	Human Prostate BPH, re-excision	Human Prostate BPH				Uni-ZAP XR
H0384	Brain, Kozak	Human Brain				pCMV Sport I
H0386	Leukocyte and Lung; 4 screens	Human Leukocytes	Blood	Cell Line		pCMV Sport I
H0390	Human Amygdala Depression, re-excision	Human Amygdala Depression			disease	pBluescript
H0392	H. Meningima, M1	Human Meningima	brain			pSport I
H0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0394	A-14 cell line	Redd-Sternberg cell				ZAP Express
H0399	Human Kidney Cortex, re-rescue	Human Kidney Cortex				Lambda ZAP II
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0404	H. Umbilical Vein endothelial cells, uninduced	HUVE Cells	Umbilical vein	Cell Line		Uni-ZAP XR
H0405	Human Pituitary, subtracted VI	Human Pituitary				pBluescript
H0406	H Amygdala Depression, subtracted	Human Amygdala Depression				Uni-ZAP XR
H0408	Human kidney Cortex, subtracted	Human Kidney Cortex				pBluescript
H0409	H. Striatum Depression, subtracted	Human Brain, Striatum Depression	Brain			pBluescript
H0410	H. Male bladder, adult	H Male Bladder, Adult	Bladder			pSport I
H0411	H Female Bladder, Adult	Human Female Adult Bladder	Bladder			pSport I
H0412	Human umbilical vein endothelial cells, IL-4 induced	HUVE Cells	Umbilical vein	Cell Line		pSport I

H0413	Human Umbilical Vein Endothelial Cells, uninduced	HUVE Cells	Umbilical vein	Cell Line		pSport1
H0415	H. Ovarian Tumor, II, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pCMVSPORT 2.0
H0416	Human Neutrophils, Activated, re-excision	Human Neutrophil - Activated	Blood	Cell Line		pBluescript
H0417	Human Pituitary, subtracted VIII	Human Pituitary				pBluescript
H0418	Human Pituitary, subtracted VII	Human Pituitary				pBluescript
H0421	Human Bone Marrow, re-excision	Bone Marrow				pBluescript
H0422	T-Cell PHA 16 hrs	T-Cells	Blood	Cell Line		pSport1
H0423	T-Cell PHA 24 hrs	T-Cells	Blood	Cell Line		pSport1
H0424	Human Pituitary, sub IX	Human Pituitary				pBluescript
H0427	Human Adipose	Human Adipose, left hipipoma				pSport1
H0428	Human Ovary	Human Ovary Tumor	Ovary			pSport1
H0429	K562 + PMA (36 hrs), re-excision	K562 Cell line	cell line	Cell Line		ZAP Express
H0431	H. Kidney Medulla, re-excision	Kidney medulla	Kidney			pBluescript
H0433	Human Umbilical Vein Endothelial cells, frac B, re-excision	HUVE Cells	Umbilical vein	Cell Line		pBluescript
H0435	Ovarian Tumor 10-3-95	Ovarian Tumor, OV350721	Ovary			pCMVSPORT 2.0
H0436	Resting T-Cell Library, II	T-Cells	Blood	Cell Line		pSport1
H0437	H Umbilical Vein Endothelial Cells, frac A, re-excision	HUVE Cells	Umbilical vein	Cell Line		Lambda ZAP II
H0438	H. Whole Brain #2, re-excision	Human Whole Brain #2				ZAP Express

H0439	Human Eosinophils	Eosinophils				pBluescript
H0441	H. Kidney Cortex, subtracted	Kidney cortex	Kidney			pBluescript
H0444	Spleen metastatic melanoma	Spleen, Metastatic malignant melanoma	Spleen		disease	pSportl
H0445	Spleen, Chronic lymphocytic leukemia	Human Spleen, CLL	Spleen		disease	pSportl
H0449	CD34+ cell, I	CD34 positive cells				pSportl
H0455	H. Striatum Depression, subt	Human Brain, Striatum Depression	Brain			pBluescript
H0457	Human Eosinophils	Human Eosinophils				pSportl
H0458	CD34+ cell, I, frac II	CD34 positive cells				pSportl
H0459	CD34+cells, II, FRACTION 2	CD34 positive cells				pCMVSPORT 2.0
H0461	H. Kidney Medulla, subtracted	Kidney medulla	Kidney			pBluescript
H0477	Human Tonsil, Lib 3	Human Tonsil	Tonsil			pSportl
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSportl
H0483	Breast Cancer cell line, MDA 36	Breast Cancer Cell line, MDA 36				pSportl
H0484	Breast Cancer Cell line, angiogenic	Breast Cancer Cell line, Angiogenic, 36T3				pSportl
H0485	Hodgkin's Lymphoma I	Hodgkin's Lymphoma I			disease	pCMVSPORT 2.0
H0486	Hodgkin's Lymphoma II	Hodgkin's Lymphoma II			disease	pCMVSPORT 2.0
H0488	Human Tonsils, Lib 2	Human Tonsils				pCMVSPORT 2.0
H0489	Crohn's Disease	Ileum	Intestine		disease	pSportl
H0492	HL-60, RA 4h, Subtracted	HL-60 Cells, RA stimulated for 4H	Blood	Cell Line		Uni-ZAP XR
H0494	Keratinocyte	Keratinocyte				pCMVSPORT 2.0
H0497	HEL cell line	HEL cell line		HEL 92.1.7		pSportl
H0505	Human Astrocyte	Human Astrocyte				pSportl
H0506	Ulcerative Colitis	Colon	Colon			pSportl
H0509	Liver, Hepatoma	Human Liver, Hepatoma,	Liver		disease	pCMVSPORT 3.0

		patient 8									
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver								pCMVSPORT 3.0
H0518	pBMC stimulated w/ poly I/C	pBMC stimulated with poly I/C									pCMVSPORT 3.0
H0519	NTERA2, control	NTERA2, Teratocarcinoma cell line									pCMVSPORT 3.0
H0520	NTERA2 + retinoic acid, 14 days	NTERA2, Teratocarcinoma cell line									pSportI
H0521	Primary Dendritic Cells, lib 1	Primary Dendritic cells									pCMVSPORT 3.0
H0522	Primary Dendritic cells, frac 2	Primary Dendritic cells									pCMVSPORT 3.0
H0525	PCR, pBMC I/C treated	pBMC stimulated with poly I/C									PCR II
H0529	Myeloid Progenitor Cell Line	TF-1 Cell Line; Myeloid progenitor cell line									pCMVSPORT 3.0
H0530	Human Dermal Endothelial Cells, untreated	Human Dermal Endothelial Cells; untreated									pSportI
H0537	H. Primary Dendritic Cells, lib 3	Primary Dendritic cells									pCMVSPORT 2.0
H0538	Merkel Cells	Merkel cells	Lymph node								pSportI
H0539	Pancreas Islet Cell Tumor	Pancreas Islet Cell Tumour	Pancreas						disease		pSportI
H0542	T Cell helper I	Helper T cell									pCMVSPORT 3.0
H0543	T cell helper II	Helper T cell									pCMVSPORT 3.0
H0544	Human endometrial stromal cells	Human endometrial stromal cells									pCMVSPORT 3.0
H0545	Human endometrial stromal cells-treated with progesterone	Human endometrial stromal cells-treated with proge									pCMVSPORT 3.0
H0546	Human endometrial stromal cells-treated with estradiol	Human endometrial stromal cells-treated with estra									pCMVSPORT 3.0



H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)	NTERA2, Teratocarcinoma cell line				pSport1
H0549	H. Epididymus, caput & corpus	Human Epididymus, caput and corpus				Uni-ZAP XR
H0550	H. Epididymus, cauda	Human Epididymus, cauda				Uni-ZAP XR
H0551	Human Thymus Stromal Cells	Human Thymus Stromal Cells				pCMVSPORT 3.0
H0553	Human Placenta	Human Placenta				pCMVSPORT 3.0
H0555	Rejected Kidney, lib 4	Human Rejected Kidney	Kidney		disease	pCMVSPORT 3.0
H0556	Activated T-cell(12h)/Thiouridine-re-excision	T-Cells	Blood		Cell Line	Uni-ZAP XR
H0559	HL-60, PMA 4H, re-excision	HL-60 Cells, PMA stimulated 4H	Blood		Cell Line	Uni-ZAP XR
H0560	KMH2	KMH2				pCMVSPORT 3.0
H0561	L428	L428				pCMVSPORT 3.0
H0563	Human Fetal Brain, normalized 50021F	Human Fetal Brain				pCMVSPORT 2.0
H0564	Human Fetal Brain, normalized C5001F	Human Fetal Brain				pCMVSPORT 2.0
H0566	Human Fetal Brain, normalized c50F	Human Fetal Brain				pCMVSPORT 2.0
H0567	Human Fetal Brain, normalized A5002F	Human Fetal Brain				pCMVSPORT 2.0
H0569	Human Fetal Brain, normalized CO	Human Fetal Brain				pCMVSPORT 2.0
H0570	Human Fetal Brain, normalized C500H	Human Fetal Brain				pCMVSPORT 2.0
H0571	Human Fetal Brain, normalized C500HE	Human Fetal Brain				pCMVSPORT 2.0
H0572	Human Fetal Brain, normalized AC5002	Human Fetal Brain				pCMVSPORT 2.0

H0574	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0575	Human Adult Pulmonary; re-excision	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0576	Resting T-Cell; re-excision	T-Cells	Blood	Cell Line		Lambda ZAP II
H0578	Human Fetal Thymus	Fetal Thymus	Thymus			pSport I
H0580	Dendritic cells, pooled	Pooled dendritic cells				pCMV Sport 3.0
H0581	Human Bone Marrow, treated	Human Bone Marrow	Bone Marrow			pCMV Sport 3.0
H0583	B Cell lymphoma	B Cell Lymphoma	B Cell		disease	pCMV Sport 3.0
H0585	Activated T-Cells, 12 hrs, re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0586	Healing groin wound, 6.5 hours post incision	healing groin wound, 6.5 hours post incision - 2/	groin		disease	pCMV Sport 3.0
H0587	Healing groin wound; 7.5 hours post incision	Groin-2/19/97	groin		disease	pCMV Sport 3.0
H0589	CD34 positive cells (cord blood), re-ex	CD34 Positive Cells	Cord Blood			ZAP Express
H0590	Human adult small intestine, re-excision	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0591	Human T-cell lymphoma; re-excision	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0592	Healing groin wound - zero hr post-incision (control)	HGS wound healing project; abdomen			disease	pCMV Sport 3.0
H0593	Olfactory epithelium; nasalcavity	Olfactory epithelium from roof of left nasal cavity				pCMV Sport 3.0
H0594	Human Lung Cancer; re-excision	Human Lung Cancer	Lung		disease	Lambda ZAP II
H0595	Stomach cancer (human); re-excision	Stomach Cancer - 5383A (human)			disease	Uni-ZAP XR
H0596	Human Colon Cancer; re-excision	Human Colon Cancer	Colon			Lambda ZAP II
H0597	Human Colon; re-excision	Human Colon				Lambda ZAP II

H0598	Human Stomach; re-excision	Human Stomach	Stomach			Uni-ZAP XR
H0599	Human Adult Heart; re-excision	Human Adult Heart	Heart			Uni-ZAP XR
H0600	Healing Abdomen wound; 70&90 min post incision	Abdomen			disease	pCMV Sport 3.0
H0601	Healing Abdomen Wound; 15 days post incision	Abdomen			disease	pCMV Sport 3.0
H0604	Human Pituitary, re-excision	Human Pituitary				pBluescript
H0606	Human Primary Breast Cancer; re-excision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0610	H. Leukocytes, normalized cot 5A	H. Leukocytes				pCMV Sport 1
H0611	H. Leukocytes, normalized cot 500 B	H. Leukocytes				pCMV Sport 1
H0613	H. Leukocytes, normalized cot 5B	H. Leukocytes				pCMV Sport 1
H0614	H. Leukocytes, normalized cot 500 A	H. Leukocytes				pCMV Sport 1
H0615	Human Ovarian Cancer Reexcision	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0616	Human Testes, Reexcision	Human Testes	Testis			Uni-ZAP XR
H0617	Human Primary Breast Cancer Reexcision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0618	Human Adult Testes, Large Inserts, Reexcision	Human Adult Testis	Testis			Uni-ZAP XR
H0619	Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0620	Human Fetal Kidney; Reexcision	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0622	Human Pancreas Tumor;	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR

	Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein				
H0623	Human Umbilical Vein; Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein				Uni-ZAP XR
H0624	12 Week Early Stage Human II; Reexcision	Twelve Week Old Early Stage Human	Embryo				Uni-ZAP XR
H0625	Ku 812F Basophils Line	Ku 812F Basophils					pSport1
H0626	Saos2 Cells; Untreated	Saos2 Cell Line; Untreated					pSport1
H0627	Saos2 Cells; Vitamin D3 Treated	Saos2 Cell Line; Vitamin D3 Treated					pSport1
H0628	Human Pre-Differentiated Adipocytes	Human Pre-Differentiated Adipocytes					Uni-ZAP XR
H0631	Saos2, Dexamethosone Treated	Saos2 Cell Line; Dexamethosone Treated					pSport1
H0632	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver				Lambda ZAP II
H0633	Lung Carcinoma A549 TNFalpha activated	TNFalpha activated A549-- Lung Carcinoma				disease	pSport1
H0634	Human Testes Tumor, re-excision	Human Testes Tumor	Testis			disease	Uni-ZAP XR
H0635	Human Activated T-Cells, re-excision	Activated T-Cells	Blood		Cell Line		Uni-ZAP XR
H0637	Dendritic Cells From CD34 Cells	Dendritic cells from CD34 cells					pSport1
H0638	CD40 activated monocyte dendritic cells	CD40 activated monocyte dendritic cells					pSport1
H0640	Ficoll Human Stromal Cells, Untreated	Ficoll Human Stromal Cells, Untreated					Other
H0641	LPS activated derived dendritic cells	LPS activated monocyte derived dendritic cells					pSport1
H0642	Hep G2 Cells, lambda library	Hep G2 Cells					Other
H0643	Hep G2 Cells, PCR library	Hep G2 Cells					Other
H0644	Human Placenta (re-	Human Placenta	Placenta				Uni-ZAP XR



	differentiated carcinoma	Breast cancer			disease	pSportI
H0661	Breast, Cancer: (4004943 A5)	Breast cancer				pSportI
H0662	Breast, Normal: (4005522B2)	Normal Breast - #4005522(B2)	Breast			pSportI
H0663	Breast, Cancer: (4005522 A2)	Breast Cancer - #4005522(A2)	Breast		disease	pSportI
H0664	Breast, Cancer: (9806C012R)	Breast Cancer	Breast		disease	pSportI
H0665	Stromal cells 3.88	Stromal cells 3.88				pSportI
H0666	Ovary, Cancer: (4004332 A2)	Ovarian Cancer, Sample #4004332A2			disease	pSportI
H0667	Stromal cells(HBM3.18)	Stromal cell(HBM 3.18)				pSportI
H0668	stromal cell clone 2.5	stromal cell clone 2.5				pSportI
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	Ovarian Cancer - 4004650A3				pSportI
H0672	Ovary, Cancer: (4004576 A8)	Ovarian Cancer(4004576A8)	Ovary			pSportI
H0673	Human Prostate Cancer, Stage B2; re-excision	Human Prostate Cancer, stage B2	Prostate			Uni-ZAP XR
H0674	Human Prostate Cancer, Stage C; re-excision	Human Prostate Cancer, stage C	Prostate			Uni-ZAP XR
H0675	Colon, Cancer: (9808C064R)	Colon Cancer 9808C064R				pCMVSPORT 3.0
H0677	TNFR degenerate oligo	B-Cells				PCRII
H0678	screened clones from placental library	Placenta	Placenta			Other
H0682	Serous Papillary Adenocarcinoma	serous papillary adenocarcinoma (9606G304SPA3B)				pCMVSPORT 3.0
H0683	Ovarian Serous Papillary	Serous papillary				pCMVSPORT 3.0

	Adenocarcinoma	adenocarcinoma, stage 3C (9804G01)				
H0684	Serous Papillary Adenocarcinoma	Ovarian Cancer-9810G606	Ovaries			pCMVSPORT 3.0
H0685	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-3	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-3				pCMVSPORT 3.0
H0686	Adenocarcinoma of Ovary, Human Cell Line	Adenocarcinoma of Ovary, Human Cell Line, # SW-626				pCMVSPORT 3.0
H0687	Human normal ovary(#9610G215)	Human normal ovary(#9610G215)	Ovary			pCMVSPORT 3.0
H0688	Human Ovarian Cancer(#9807G017)	Human Ovarian cancer(#9807G017),mRNA from Maura Ru				pCMVSPORT 3.0
H0689	Ovarian Cancer	Ovarian Cancer, #9806G019				pCMVSPORT 3.0
H0690	Ovarian Cancer, # 9702G001	Ovarian Cancer, #9702G001				pCMVSPORT 3.0
H0691	Normal Ovary, #9710G208	normal ovary, #9710G208				pCMVSPORT 3.0
H0693	Normal Prostate #ODQ3958EN	Normal Prostate Tissue # ODQ3958EN				pCMVSPORT 3.0
H0694	Prostate gland adenocarcinoma	Prostate gland, adenocarcinoma, mod/diff, gleason	prostate gland			pCMVSPORT 3.0
H0695	mononucleocytes from patient	mononucleocytes from patient at Shady Grove Hospit				pCMVSPORT 3.0
N0009	Human Hippocampus, prescreened	Human Hippocampus				
S0001	Brain frontal cortex	Brain frontal cortex	Brain			Lambda ZAP II
S0002	Monocyte activated	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0003	Human Osteoclastoma	Osteoclastoma	bone		disease	Uni-ZAP XR
S0004	Prostate	Prostate BPH	Prostate			Lambda ZAP II
S0005	Heart	Heart-left ventricle	Heart			pCDNA

S0006	Neuroblastoma	Human Neural Blastoma					pCDNA
S0007	Early Stage Human Brain	Human Fetal Brain					Uni-ZAP XR
S0010	Human Amygdala	Amygdala					Uni-ZAP XR
S0011	STROMAL - OSTEOCLASTOMA	Osteoclastoma	bone			disease	Uni-ZAP XR
S0014	Kidney Cortex	Kidney cortex	Kidney				Uni-ZAP XR
S0015	Kidney medulla	Kidney medulla	Kidney				Uni-ZAP XR
S0016	Kidney Pyramids	Kidney pyramids	Kidney				Uni-ZAP XR
S0022	Human Osteoclastoma Stromal Cells - unamplified	Osteoclastoma Stromal Cells					Uni-ZAP XR
S0024	Human Kidney Medulla - unamplified	Human Kidney Medulla					
S0026	Stromal cell TF274	stromal cell	Bone marrow		Cell Line		Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmonary artery		Cell Line		Uni-ZAP XR
S0028	Smooth muscle, control	Smooth muscle	Pulmonary artery		Cell Line		Uni-ZAP XR
S0029	brain stem	Brain stem	brain				Uni-ZAP XR
S0030	Brain pons	Brain Pons	Brain				Uni-ZAP XR
S0031	Spinal cord	Spinal cord	spinal cord				Uni-ZAP XR
S0032	Smooth muscle-IL1b induced	Smooth muscle	Pulmonary artery		Cell Line		Uni-ZAP XR
S0036	Human Substantia Nigra	Human Substantia Nigra					Uni-ZAP XR
S0037	Smooth muscle, IL1b induced	Smooth muscle	Pulmonary artery		Cell Line		Uni-ZAP XR
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb	Human Whole Brain #2					ZAP Express
S0039	Hypothalamus	Hypothalamus	Brain				Uni-ZAP XR
S0040	Adipocytes	Human Adipocytes from Osteoclastoma					Uni-ZAP XR
S0044	Prostate BPH	prostate BPH	Prostate			disease	Uni-ZAP XR
S0045	Endothelial cells-control	Endothelial cell	endothelial cell-lung		Cell Line		Uni-ZAP XR



S0046	Endothelial-induced	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0048	Human Hypothalamus, Alzheimer's	Human Hypothalamus, Alzheimer's			disease	Uni-ZAP XR
S0049	Human Brain, Striatum	Human Brain, Striatum				Uni-ZAP XR
S0050	Human Frontal Cortex, Schizophrenia	Human Frontal Cortex, Schizophrenia			disease	Uni-ZAP XR
S0051	Human Hypothalamus, Schizophrenia	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0052	neutrophils control	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0053	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0106	STRIATUM DEPRESSION		BRAIN		disease	Uni-ZAP XR
S0110	Brain Amygdala Depression		Brain		disease	Uni-ZAP XR
S0112	Hypothalamus		Brain			Uni-ZAP XR
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0116	Bone marrow	Bone marrow	Bone marrow			Uni-ZAP XR
S0122	Osteoclastoma-normalized A	Osteoclastoma	bone		disease	pBluescript
S0124	Smooth muscle-edited A	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0126	Osteoblasts	Osteoblasts	Knee	Cell Line		Uni-ZAP XR
S0132	Epithelial-TNF $\alpha$ and INF induced	Airway Epithelial				Uni-ZAP XR
S0134	Apoptotic T-cell	apoptotic cells		Cell Line		Uni-ZAP XR
S0136	PERM TF274	stromal cell	Bone marrow	Cell Line		Lambda ZAP II
S0140	eosinophil-IL5 induced	eosinophil	lung	Cell Line		Uni-ZAP XR
S0142	Macrophage-oxLDL	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0144	Macrophage (GM-CSF treated)	Macrophage (GM-CSF treated)				Uni-ZAP XR

S0146	prostate-edited	prostate BPH	Prostate			Uni-ZAP XR
S0148	Normal Prostate	Prostate	prostate			Uni-ZAP XR
S0150	LNCAP prostate cell line	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
S0152	PC3 Prostate cell line	PC3 prostate cell line				Uni-ZAP XR
S0180	Bone Marrow Stroma, TNF&LPS ind	Bone Marrow Stroma, TNF & LPS induced			disease	Uni-ZAP XR
S0190	Prostate BPH, Lib 2, subtraced	Human Prostate BPH				pSport1
S0192	Synovial Fibroblasts (control)	Synovial Fibroblasts				pSport1
S0194	Synovial hypoxia	Synovial Fibroblasts				pSport1
S0196	Synovial IL-1/TNF stimulated	Synovial Fibroblasts				pSport1
S0206	Smooth Muscle- HASTE normalized	Smooth muscle	Pulmonary artery	Cell Line		pBluescript
S0210	Mesangial cell, frac 2	Mesangial cell				pSport1
S0212	Bone Marrow Stromal Cell, untreated	Bone Marrow Stromal Cell, untreated				pSport1
S0214	Human Osteoclastoma, re-excision	Osteoclastoma	bone		disease	Uni-ZAP XR
S0216	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0218	Apoptotic T-cell, re-excision	apoptotic cells		Cell Line		Uni-ZAP XR
S0220	H. hypothalamus, frac A; re-excision	Hypothalamus	Brain			ZAP Express
S0222	H. Frontal cortex, epileptic; re-excision	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S0242	Synovial Fibroblasts (III/TNF), sub	Synovial Fibroblasts				pSport1
S0250	Human Osteoblasts II	Human Osteoblasts	Femur		disease	pCMV Sport 2.0
S0260	Spinal Cord, re-excision	Spinal cord	spinal cord			Uni-ZAP XR
S0276	Synovial hypoxia-RSF	Synovial fibroblasts	Synovial tissue			pSport1

	subtracted	(rheumatoid)				
S0278	H Macrophage (GM-CSF treated), re-excision	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0280	Human Adipose Tissue, re-excision	Human Adipose Tissue				Uni-ZAP XR
S0282	Brain Frontal Cortex, re-excision	Brain frontal cortex	Brain			Lambda ZAP II
S0294	Larynx tumor	Larynx tumor	Larynx, vocal cord	disease		pSportI
S0298	Bone marrow stroma, treated	Bone marrow stroma, treated SB	Bone marrow			pSportI
S0300	Frontal lobe, dementia; re-excision	Frontal Lobe dementia/Alzheimer's	Brain			Uni-ZAP XR
S0312	Human osteoarthritic; fraction II	Human osteoarthritic cartilage		disease		pSportI
S0314	Human osteoarthritic; fraction I	Human osteoarthritic cartilage		disease		pSportI
S0328	Palate carcinoma	Palate carcinoma	Uvula	disease		pSportI
S0330	Palate normal	Palate normal	Uvula			pSportI
S0332	Pharynx carcinoma	Pharynx carcinoma	Hypopharynx			pSportI
S0334	Human Normal Cartilage Fraction III	Human Normal Cartilage				pSportI
S0336	Human Normal Cartilage Fraction IV	Human Normal Cartilage				pSportI
S0338	Human Osteoarthritic Cartilage Fraction III	Human osteoarthritic cartilage		disease		pSportI
S0342	Adipocytes; re-excision	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0344	Macrophage-oxLDL; re-excision	macrophage-oxidized LDL treated	blood		Cell Line	Uni-ZAP XR
S0346	Human Amygdala; re-excision	Amygdala				Uni-ZAP XR
S0350	Pharynx Carcinoma	Pharynx carcinoma	Hypopharynx	disease		pSportI

S0354	Colon Normal II	Colon Normal	Colon			pSportl
S0356	Colon Carcinoma	Colon Carcinoma	Colon	disease		pSportl
S0358	Colon Normal III	Colon Normal	Colon			pSportl
S0360	Colon Tumor II	Colon Tumor	Colon	disease		pSportl
S0364	Human Quadriceps	Quadriceps muscle				pSportl
S0366	Human Soleus	Soleus Muscle				pSportl
S0368	Human Pancreatic Langerhans	Islets of Langerhans				pSportl
S0372	Larynx carcinoma III	Larynx carcinoma		disease		pSportl
S0374	Normal colon	Normal colon				pSportl
S0376	Colon Tumor	Colon Tumor		disease		pSportl
S0378	Pancreas normal PCA4 No	Pancreas Normal PCA4 No				pSportl
S0380	Pancreas Tumor PCA4 Tu	Pancreas Tumor PCA4 Tu		disease		pSportl
S0386	Human Whole Brain, re-excision	Whole brain	Brain			ZAP Express
S0388	Human Hypothalamus, schizophrenia, re-excision	Human Hypothalamus, Schizophrenia		disease		Uni-ZAP XR
S0390	Smooth muscle; control; re-excision	Smooth muscle	Pulmonary artery		Cell Line	Uni-ZAP XR
S0392	Salivary Gland	Salivary gland; normal				pSportl
S0394	Stomach; normal	Stomach; normal				pSportl
S0398	Testis; normal	Testis; normal				pSportl
S0404	Rectum normal	Rectum, normal				pSportl
S0406	Rectum tumour	Rectum tumour				pSportl
S0408	Colon, normal	Colon, normal				pSportl
S0410	Colon, tumour	Colon, tumour				pSportl
S0412	Temporal cortex-Alzheimer; subtracted	Temporal cortex, alzheimer		disease		Other
S0414	Hippocampus, Alzheimer Subtracted	Hippocampus, Alzheimer Subtracted				Other
S0418	CHME Cell Line; treated 5	CHME Cell Line; treated				pCMV Sport 3.0

	hrs							
S0420	CHME Cell Line, untreated	CHME Cell line, untreated						pSportl
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)	Mo7e Cell Line GM-CSF treated (1ng/ml)						pCMVSPORT 3.0
S0424	TF-1 Cell Line GM-CSF Treated	TF-1 Cell Line GM-CSF Treated						pSportl
S0426	Monocyte activated; re-excision	Monocyte-activated	blood		Cell Line			Uni-ZAP XR
S0428	Neutrophils control; re-excision	human neutrophils	blood		Cell Line			Uni-ZAP XR
S0430	Aryepiglottis Normal	Aryepiglottis Normal						pSportl
S0432	Sinus piniformis Tumour	Sinus piniformis Tumour						pSportl
S0434	Stomach Normal	Stomach Normal				disease		pSportl
S0436	Stomach Tumour	Stomach Tumour				disease		pSportl
S0438	Liver Normal Met5No	Liver Normal Met5No						pSportl
S0440	Liver Tumour Met 5 Tu	Liver Tumour						pSportl
S0442	Colon Normal	Colon Normal						pSportl
S0444	Colon Tumor	Colon Tumour				disease		pSportl
S0446	Tongue Tumour	Tongue Tumour						pSportl
S0448	Larynx Normal	Larynx Normal						pSportl
S0450	Larynx Tumour	Larynx Tumour						pSportl
S0452	Thymus	Thymus						pSportl
S0454	Placenta	Placenta	Placenta					pSportl
S0456	Tongue Normal	Tongue Normal						pSportl
S0458	Thyroid Normal (SDCA2 No)	Thyroid normal						pSportl
S0460	Thyroid Tumour	Thyroid Tumour						pSportl
S0462	Thyroid Thyroiditis	Thyroid Thyroiditis						pSportl
S0470	Adenocarcinoma	PYFD				disease		pSportl
S0472	Lung Mesothelium	PYBT						pSportl
S0474	Human blood platelets	Platelets	Blood platelets					Other
S0665	Human Amygdala; re-	Amygdala						Uni-ZAP XR

	excision						
S3012	Smooth Muscle Serum Treated, Norm	Smooth muscle	Pulmonary artery	Cell Line			pBluescript
S3014	Smooth muscle, serum induced, re-exc	Smooth muscle	Pulmonary artery	Cell Line			pBluescript
S6014	H. hypothalamus, frac A	Hypothalamus	Brain				ZAP Express
S6022	H. Adipose Tissue	Human Adipose Tissue					Uni-ZAP XR
S6024	Alzheimers, spongy change	Alzheimer's/spongy change	Brain		disease		Uni-ZAP XR
S6026	Frontal Lobe, Dementia	Frontal Lobe dementia/Alzheimer's	Brain				Uni-ZAP XR
S6028	Human Manic Depression Tissue	Human Manic depression tissue	Brain		disease		Uni-ZAP XR
T0002	Activated T-cells	Activated T-Cell, PBL fraction	Blood	Cell Line			pBluescript SK-
T0004	Human White Fat	Human White Fat					pBluescript SK-
T0006	Human Pineal Gland	Human Pineal Gland					pBluescript SK-
T0007	Colon Epithelium	Colon Epithelium					pBluescript SK-
T0008	Colorectal Tumor	Colorectal Tumor			disease		pBluescript SK-
T0010	Human Infant Brain	Human Infant Brain					Other
T0023	Human Pancreatic Carcinoma	Human Pancreatic Carcinoma			disease		pBluescript SK-
T0039	HSA 172 Cells	Human HSA 172 cell line					pBluescript SK-
T0040	HSC172 cells	SA172 Cells					pBluescript SK-
T0041	Jurkat T-cell G1 phase	Jurkat T-cell					pBluescript SK-
T0042	Jurkat T-Cell, S phase	Jurkat T-Cell Line					pBluescript SK-
T0048	Human Aortic Endothelium	Human Aortic Endothelium					pBluescript SK-
T0049	Aorta endothelial cells + TNF-a	Aorta endothelial cells					pBluescript SK-
T0060	Human White Adipose	Human White Fat					pBluescript SK-
T0067	Human Thyroid	Human Thyroid					pBluescript SK-
T0068	Normal Ovary, Premenopausal	Normal Ovary, Premenopausal					pBluescript SK-

T0069	Human Uterus, normal	Human Uterus, normal					pBluescript SK-
T0071	Human Bone Marrow	Human Bone Marrow					pBluescript SK-
T0082	Human Adult Retina	Human Adult Retina					pBluescript SK-
T0103	Human colon carcinoma (HCC) cell line						pBluescript SK-
T0104	HCC cell line metastasis to liver						pBluescript SK-
T0109	Human (HCC) cell line liver (mouse) metastasis, remake						pBluescript SK-
T0110	Human colon carcinoma (HCC) cell line, remake						pBluescript SK-
T0114	Human (Caco-2) cell line, adenocarcinoma, colon, remake						pBluescript SK-
T0115	Human Colon Carcinoma (HCC) cell line						pBluescript SK-
L0002	Atrium cDNA library Human heart						
L0005	Clontech human aorta polyA+ mRNA (#6572)						
L0015	Human						
L0018	Human (M.Lovett)						
L0021	Human adult (K.Okubo)						
L0022	Human adult lung 3" directed Mbol cDNA						
L0041	Human epidermal keratinocyte						
L0045	Human keratinocyte differential display (B.Lin)						
L0053	Human pancreatic tumor						
L0055	Human promyelocyte						
L0060	Human thymus NSTH II						

L0065	Liver HepG2 cell line.						
L0070	Selected chromosome 21 cDNA library						
L0142	Human placenta cDNA (TFujiwara)	placenta					
L0143	Human placenta polyA+ (TFujiwara)	placenta					
L0157	Human fetal brain (TFujiwara)		brain				
L0163	Human heart cDNA (YNakamura)		heart				
L0183	Human HeLa cells (M.Lovett)			HeLa			
L0194	Human pancreatic cancer cell line Patu 8988t	pancreatic cancer		Patu 8988t			
L0351	Infant brain, Bento Soares						BA, M13-derived
L0352	Normalized infant brain, Bento Soares						BA, M13-derived
L0355	P, Human foetal Brain Whole tissue						Bluescript
L0356	S, Human foetal Adrenals tissue						Bluescript
L0361	Stratagene ovary (#937217)		ovary				Bluescript SK
L0362	Stratagene ovarian cancer (#937219)						Bluescript SK-
L0363	NCI CGAP_GC2	germ cell tumor					Bluescript SK-
L0364	NCI CGAP_GC5	germ cell tumor					Bluescript SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe					Bluescript SK-
L0367	NCI CGAP_Sch1	Schwannoma tumor					Bluescript SK-
L0369	NCI CGAP_AAI	adrenal adenoma	adrenal gland				Bluescript SK-
L0370	Johnston frontal cortex	pooled frontal lobe	brain				Bluescript SK-



L0371	NCI CGAP Br3	breast tumor	breast			Bluescript SK-
L0372	NCI CGAP Co12	colon tumor	colon			Bluescript SK-
L0373	NCI CGAP Co11	tumor	colon			Bluescript SK-
L0374	NCI CGAP Co2	tumor	colon			Bluescript SK-
L0375	NCI CGAP Kid6	kidney tumor	kidney			Bluescript SK-
L0376	NCI CGAP Lar1	larynx	larynx			Bluescript SK-
L0378	NCI CGAP Lu1	lung tumor	lung			Bluescript SK-
L0381	NCI CGAP HN4	squamous cell carcinoma	pharynx			Bluescript SK-
L0382	NCI CGAP Pr25	epithelium (cell line)	prostate			Bluescript SK-
L0383	NCI CGAP Pr24	invasive tumor (cell line)	prostate			Bluescript SK-
L0384	NCI CGAP Pr23	prostate tumor	prostate			Bluescript SK-
L0386	NCI CGAP HN3	squamous cell carcinoma from base of tongue	tongue			Bluescript SK-
L0388	NCI CGAP HN6	normal gingiva (cell line from immortalized kerati				Bluescript SK-
L0411	1-NIB					Lafmid BA
L0415	b4HB3MA Cot8-HAP-Ft					Lafmid BA
L0435	Infant brain, LLNL array of Dr. M. Soares INIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA
L0439	Soares infant brain INIB		whole brain			Lafmid BA
L0454	Clontech adult human fat cell library HL1108A					lambda gt10
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0456	Human retina cDNA Tsp509I-cleaved sublibrary	retina	eye			lambda gt10
L0463	fetal brain cDNA	brain	brain			lambda gt11
L0465	TEST1, Human adult Testis tissue					lambda nm1149
L0471	Human fetal heart, Lambda					Lambda ZAP Express

	ZAP Express						
L0475	KG1-a Lambda Zap Express cDNA library					KG1-a	Lambda Zap Express (Stratagene)
L0476	Fetal brain, Stratagene						Lambda ZAP II
L0480	Stratagene cat#937212 (1992)						Lambda ZAP, pBluescript SK(-)
L0481	CD34+DIRECTIONAL						Lambda ZAPII
L0483	Human pancreatic islet						Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.				leg muscle		Lambda ZAPII
L0492	Human Genomic						pAMP
L0493	NCI CGAP_Ov26				ovary		pAMP1
L0497	NCI CGAP_HSC4				bone marrow		pAMP1
L0499	NCI CGAP_HSC2				bone marrow		pAMP1
L0500	NCI CGAP_Brm20				brain		pAMP1
L0503	NCI CGAP_Br17				breast		pAMP1
L0506	NCI CGAP_Br16				breast		pAMP1
L0509	NCI CGAP_Lu26				lung		pAMP1
L0510	NCI CGAP_Ov33				ovary		pAMP1
L0511	NCI CGAP_Ov34				ovary		pAMP1
L0514	NCI CGAP_Ov31				ovary		pAMP1
L0515	NCI CGAP_Ov32				ovary		pAMP1
L0517	NCI CGAP_Pr1						pAMP10
L0518	NCI CGAP_Pr2						pAMP10
L0519	NCI CGAP_Pr3						pAMP10
L0520	NCI CGAP_Alv1						pAMP10
L0521	NCI CGAP_Ew1						pAMP10
L0522	NCI CGAP_Kid1						pAMP10
L0523	NCI CGAP_Lip2						pAMP10
L0526	NCI CGAP_Pr12						pAMP10

		lesion				
L0527	NCI CGAP Ov2	ovary				pAMP10
L0528	NCI CGAP_Pr5	prostate				pAMP10
L0529	NCI CGAP_Pr6	prostate				pAMP10
L0530	NCI CGAP_Pr8	prostate				pAMP10
L0532	NCI CGAP_Thy1	thyroid				pAMP10
L0533	NCI CGAP_HSC1	stem cells	bone marrow			pAMP10
L0534	Chromosome 7 Fetal Brain cDNA Library	brain	brain			pAMP10
L0539	Chromosome 7 Placental cDNA Library		placenta			pAMP10
L0540	NCI CGAP_Pr10	invasive prostate tumor	prostate			pAMP10
L0542	NCI CGAP_Pr11	normal prostatic epithelial cells	prostate			pAMP10
L0543	NCI CGAP_Pr9	normal prostatic epithelial cells	prostate			pAMP10
L0544	NCI CGAP_Pr4	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0545	NCI CGAP_Pr4.1	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0553	NCI CGAP_Co22	colonic adenocarcinoma	colon			pAMP10
L0558	NCI CGAP_Ov40	endometrioid ovarian metastasis	ovary			pAMP10
L0559	NCI CGAP_Ov39	papillary serous ovarian metastasis	ovary			pAMP10
L0560	NCI CGAP_HN12	moderate to poorly differentiated invasive carcino	tongue			pAMP10
L0561	NCI CGAP_HN11	normal squamous epithelium	tongue			pAMP10
L0562	Chromosome 7 HeLa cDNA Library			HeLa cell line; ATCC		pAMP10
L0564	Jia bone marrow stroma	bone marrow stroma				pBluescript
L0565	Normal Human Trabecular	Bone	Hip			pBluescript

	Bone Cells						
L0581	Stratagene liver (#937224)						pBluescript SK
L0586	HTCDL1					liver	pBluescript SK(-)
L0588	Stratagene endothelial cell 937223						pBluescript SK-
L0589	Stratagene fetal retina 937202						pBluescript SK-
L0590	Stratagene fibroblast (#937212)						pBluescript SK-
L0591	Stratagene HeLa cell s3 937216						pBluescript SK-
L0592	Stratagene hNT neuron (#937233)						pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)						pBluescript SK-
L0594	Stratagene neuroepithelium NT2RAMI 937234						pBluescript SK-
L0595	Stratagene NT2 neuronal precursor 937230					brain	pBluescript SK-
L0596	Stratagene colon (#937204)					colon	pBluescript SK-
L0598	Morton Fetal Cochlea					ear	pBluescript SK-
L0599	Stratagene lung (#937210)					lung	pBluescript SK-
L0600	Weizmann Olfactory Epithelium					nose	pBluescript SK-
L0601	Stratagene pancreas (#937208)					pancreas	pBluescript SK-
L0602	Pancreatic Islet					pancreas	pBluescript SK-
L0603	Stratagene placenta (#937225)					placenta	pBluescript SK-
L0604	Stratagene muscle 937209					skeletal muscle	pBluescript SK-
L0605	Stratagene fetal spleen (#937205)					spleen	pBluescript SK-
L0606	NCI CGAP Lym5					lymph node	pBluescript SK-

L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0610	Schiller glioblastoma multiforme	glioblastoma multiforme	brain			pBluescript SK- (Stratagene)
L0611	Schiller meningioma	meningioma	brain			pBluescript SK- (Stratagene)
L0615	22 week old human fetal liver cDNA library					pBluescriptII SK(-)
L0617	Chromosome 22 exon					pBluescriptIIKS+
L0622	HM1					pcDNAII (Invitrogen)
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0625	NCI CGAP_AR1	bulk alveolar tumor				pCMV-SPORT2
L0629	NCI CGAP_Mel3	metastatic melanoma to bowel	bowel (skin primary)			pCMV-SPORT4
L0630	NCI CGAP_CNS1	substantia nigra	brain			pCMV-SPORT4
L0632	NCI CGAP_Li5	hepatic adenoma	liver			pCMV-SPORT4
L0633	NCI CGAP_Lu6	small cell carcinoma	lung			pCMV-SPORT4
L0634	NCI CGAP_Ov8	serous adenocarcinoma	ovary			pCMV-SPORT4
L0635	NCI CGAP_PNS1	dorsal root ganglion	peripheral nervous system			pCMV-SPORT4
L0636	NCI CGAP_Pit1	four pooled pituitary adenomas	brain			pCMV-SPORT6
L0637	NCI CGAP_Bm53	three pooled meningiomas	brain			pCMV-SPORT6
L0638	NCI CGAP_Bm35	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0639	NCI CGAP_Bm52	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0640	NCI CGAP_Br18	four pooled high-grade tumors, including two primary	breast			pCMV-SPORT6
L0641	NCI CGAP_Co17	juvenile granulosa tumor	colon			pCMV-SPORT6
L0642	NCI CGAP_Co18	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0643	NCI CGAP_Co19	moderately differentiated	colon			pCMV-SPORT6

		adenocarcinoma						
L0644	NCI_CGAP_Co20	moderately differentiated adenocarcinoma	colon					pCMV-SPORT6
L0645	NCI_CGAP_Co21	moderately differentiated adenocarcinoma	colon					pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately-differentiated adenocarcinoma	colon					pCMV-SPORT6
L0647	NCI_CGAP_Sar4	five pooled sarcomas, including myxoid liposarcoma	connective tissue					pCMV-SPORT6
L0648	NCI_CGAP_Eso2	squamous cell carcinoma	esophagus					pCMV-SPORT6
L0649	NCI_CGAP_GUI	2 pooled high-grade transitional cell tumors	genitourinary tract					pCMV-SPORT6
L0650	NCI_CGAP_Kid13	2 pooled Wilms' tumors, one primary and one metast	kidney					pCMV-SPORT6
L0651	NCI_CGAP_Kid8	renal cell tumor	kidney					pCMV-SPORT6
L0652	NCI_CGAP_Lu27	four pooled poorly-differentiated adenocarcinomas	lung					pCMV-SPORT6
L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung					pCMV-SPORT6
L0654	NCI_CGAP_Lu31		lung, cell line					pCMV-SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node					pCMV-SPORT6
L0656	NCI_CGAP_Ov38	normal epithelium	ovary					pCMV-SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled (see description)	ovary					pCMV-SPORT6
L0658	NCI_CGAP_Ov35	tumor, 5 pooled (see description)	ovary					pCMV-SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas					pCMV-SPORT6
L0661	NCI_CGAP_Mel15	malignant melanoma, metastatic to lymph node	skin					pCMV-SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated	stomach					pCMV-SPORT6

			adenocarcinoma with signet r						
L0663	NCI_CGAP_Ut2		moderately-differentiated endometrial adenocarcino	uterus					pCMV-SPORT6
L0664	NCI_CGAP_Ut3		poorly-differentiated endometrial adenocarcinoma,	uterus					pCMV-SPORT6
L0665	NCI_CGAP_Ut4		serous papillary carcinoma, high grade, 2 pooled t	uterus					pCMV-SPORT6
L0666	NCI_CGAP_Ut1		well-differentiated endometrial adenocarcinoma, 7	uterus					pCMV-SPORT6
L0667	NCI_CGAP_CML1		myeloid cells, 18 pooled CML cases, BCR/ABL rearra	whole blood					pCMV-SPORT6
L0683	Stanley Frontal NS pool 2		frontal lobe (see description)	brain					pCR2.1-TOPO (Invitrogen)
L0686	Stanley Frontal SN pool 2		frontal lobe (see description)	brain					pCR2.1-TOPO (Invitrogen)
L0690	Testis, Subtracted								pCRII
L0698	Testis 2								PGEM 5zf(+)
L0709	NIH MGC 21		choriocarcinoma	placenta					pOTB7
L0710	NIH MGC 7		small cell carcinoma	lung	MGC3				pOTB7
L0717	Gessler Wilms tumor								pSPORT1
L0718	Testis 5								pSPORT1
L0731	Soares_pregnant_uterus_N bHPU			uterus					pT7T3-Pac
L0738	Human colorectal cancer								pT7T3D
L0740	Soares melanocyte 2NbHM		melanocyte						pT7T3D (Pharmacia) with a modified polylinker
L0741	Soares adult brain N2b4HB55Y			brain					pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y			brain					pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst			breast					pT7T3D (Pharmacia) with a modified polylinker
L0744	Soares breast 3NbHBst			breast					pT7T3D (Pharmacia) with a modified polylinker

L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbHHI1 9W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_spleen_ 1NFLS S1		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0750	Soares_fetal_lung_NbHLI1 9W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tumor NbHPA	parathyroid tumor	parathyroid gland			pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_gland_N3H PG		pineal gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to9week s_2NbHP8to9W		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares_multiple_sclerosis_ 2NbHMSP	multiple sclerosis lesions				pT7T3D (Pharmacia) with a modified polylinker V TYPE
L0757	Soares_senescent_fibroblas ts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_Nb2HF 8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0761	NCI CGAP CLL1	B-cell, chronic lymphocytic leukemia				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0762	NCI CGAP Br1.1	breast				pT7T3D-Pac (Pharmacia)



L0763	NCI_CGAP_Br2	breast				with a modified polylinker pT7T3D-Pac (Pharmacia)
L0764	NCI_CGAP_Co3	colon				with a modified polylinker pT7T3D-Pac (Pharmacia)
L0766	NCI_CGAP_GCB1	germinal center B cell				with a modified polylinker pT7T3D-Pac (Pharmacia)
L0767	NCI_CGAP_GC3	pooled germ cell tumors				with a modified polylinker pT7T3D-Pac (Pharmacia)
L0768	NCI_CGAP_GC4	pooled germ cell tumors				with a modified polylinker pT7T3D-Pac (Pharmacia)
L0769	NCI_CGAP_Bm25	anaplastic oligodendroglioma		brain		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0770	NCI_CGAP_Bm23	glioblastoma (pooled)		brain		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0771	NCI_CGAP_Co8	adenocarcinoma		colon		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0772	NCI_CGAP_Co10	colon tumor RER+		colon		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0773	NCI_CGAP_Co9	colon tumor RER+		colon		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0774	NCI_CGAP_Kid3			kidney		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)		kidney		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0776	NCI_CGAP_Lu5	carcinoid		lung		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant		mixed (see below)		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0779	Soares_NFL_T_GBC_S1			pooled		with a modified polylinker pT7T3D-Pac (Pharmacia)
L0780	Soares_NSF_F8_9W_OT_PA_P_S1			pooled		with a modified polylinker pT7T3D-Pac (Pharmacia)

L0782	NCI_CGAP_Pr21	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0784	NCI_CGAP_Lei2	leiomyosarcoma	soft tissue			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0785	Barstead spleen HPLRB2		spleen			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0786	Soares_NbHFB		whole brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0788	NCI_CGAP_Sub2					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0793	NCI_CGAP_Sub7					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0796	NCI_CGAP_Brm50	medulloblastoma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell	kidney			pT7T3D-Pac (Pharmacia)

		type)						with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid		lung				pT7T3D-Pac (Pharmacia)
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4		lung				with a modified polylinker
L0807	NCI_CGAP_Ov18	fibrothoma		ovary				pT7T3D-Pac (Pharmacia)
L0809	NCI_CGAP_Pr28			prostate				with a modified polylinker
L0811	BATM2							with a modified polylinker
L0879	BT0254			breast				pTZ18
L0946	BT0333			breast				puc18
L1441	CT0249			colon				puc18
L1499	CT0322			colon				puc18
L1788	HT0229			head neck				puc18
L1877	HT0340			head neck				puc18
L1942	HT0452			head neck				puc18
L2251	Human fetal lung	Fetal lung						
L2255	GLC	corresponding non cancerous liver tissue						pBluescript sk(-)
L2257	NIH_MGC_65	adenocarcinoma		colon				pCMV-SPORT6
L2258	NIH_MGC_67	retinoblastoma		eye				pCMV-SPORT6
L2259	NIH_MGC_68	large cell carcinoma		lung				pCMV-SPORT6
L2260	NIH_MGC_69	large cell carcinoma, undifferentiated		lung				pCMV-SPORT6
L2261	NIH_MGC_70	epithelioid carcinoma		pancreas				pCMV-SPORT6
L2262	NIH_MGC_72	melanotic melanoma		skin				pCMV-SPORT6
L2263	NIH_MGC_66	adenocarcinoma		ovary				pCMV-SPORT6
L2265	NIH_MGC_39	adenocarcinoma		pancreas				pOTB7
L2270	Lupski_dorsal_root_gangli on	dorsal root ganglia						pCMV-SPORT6 (Life Technologies)
L2281	BT0701			breast				puc18

L2333	CT0417			colon			puc18
L2338	CT0432			colon			puc18
L2346	CT0483			colon			puc18
L2439	NN1022			nervous normal			puc18
L2440	NN1023			nervous normal			puc18
L2467	NN1112			nervous normal			puc18
L2477	HT0408			head neck			puc18
L2490	HT0545			head neck			puc18
L2491	HT0559			head neck			puc18
L2495	HT0594			head neck			puc18
L2504	HT0636			head neck			puc18
L2522	HT0704			head neck			puc18
L2539	HT0727			head neck			puc18
L2540	HT0728			head neck			puc18
L2562	HT0760			head neck			puc18
L2599	HT0810			head neck			puc18
L2634	HT0872			head neck			puc18
L2637	HT0877			head neck			puc18
L2651	NIH_MGC_20		melanotic melanoma	skin			pOTB7
L2653	NIH_MGC_58		hypernephroma	kidney			pDNR-LIB (Clontech)
L2654	NIH_MGC_9		adenocarcinoma cell line	ovary			pOTB7
L2655	NIH_MGC_55		from acute myelogenous leukemia	bone marrow			pDNR-LIB (Clontech)
L2657	NIH_MGC_54		from chronic myelogenous leukemia	bone marrow			pDNR-LIB (Clontech)
L2681	NT0048			nervous tumor			puc18
L2702	NT0098			nervous tumor			puc18
L2716	NT0117			nervous tumor			puc18
L2814	FT0128			prostate tumor			puc18
L2817	FT0131			prostate tumor			puc18
L2842	UM0009			uterus			puc18
L2852	UM0077			uterus			puc18

L2854	UM0091			uterus			puc18
L2865	AN0004			amnion_normal			puc18
L2884	AN0041			amnion_normal			puc18
L2902	BN0036			breast_normal			puc18
L2905	BN0046			breast_normal			puc18
L2906	BN0047			breast_normal			puc18
L2918	BN0114			breast_normal			puc18
L2919	BN0115			breast_normal			puc18
L3002	BN0276			breast_normal			puc18
L3058	EN0004			lung_normal			puc18
L3081	ET0005			lung_tumor			puc18
L3089	ET0018			lung_tumor			puc18
L3092	ET0023			lung_tumor			puc18
L3127	ET0084			lung_tumor			puc18
L3144	MT0035			marrow			puc18
L3154	MT0050			marrow			puc18
L3212	OT0076			ovary			puc18
L3255	FN0064			prostate_normal			puc18
L3311	FN0180			prostate_normal			puc18
L3312	FN0181			prostate_normal			puc18
L3316	FN0188			prostate_normal			puc18
L3327	SN0024			stomach_normal			puc18
L3330	SN0041			stomach_normal			puc18
L3352	TN0027			testis_normal			puc18
L3374	TN0070			testis_normal			puc18
L3378	TN0080			testis_normal			puc18
L3388	GKC	hepatocellular carcinoma					pBluescript sk(-)
L3391	NIH MGC 53	carcinoma, cell line		bladder			pDNR-LIB (Clontech)
L3403	AN0087			amnion_normal			puc18
L3432	CT0461			colon			puc18
L3466	GN0020			placenta_normal			puc18
L3485	GN0070			placenta_normal			puc18

L3504	HT0873		head neck		puc18
L3506	HT0879		head neck		puc18
L3521	HT0919		head neck		puc18
L3530	HT0939		head neck		puc18
L3603	UM0093		uterus		puc18
L3612	UT0011		uterus tumor		puc18
L3631	UT0072		uterus tumor		puc18
L3636	NIH MGC 73		brain		pDNR-LIB (Clontech)
L3643	ADB	Adrenal gland			pBluescript sk(-)
L3644	ADC	Adrenal gland			pBluescript sk(-)
L3645	Cu	adrenal cortico adenoma for Cushing's syndrome			pBluescript sk(-)
L3649	DCB				pTriplEx2
L3653	HTB	Hypothalamus			pBluescript sk(-)
L3655	HTC	Hypothalamus			pBluescript sk(-)
L3657	HTF	Hypothalamus			pBluescript sk(-)
L3658	cdA	pheochromocytoma			pTriplEx2
L3659	CB	cord blood			pBluescript
L3684	BT0812		breast		puc18
L3722	GN0030		placenta normal		puc18
L3811	NPC	pituitary			pBluescript sk(-)
L3813	TP	pituitary tumor			pTriplEx2
L3814	BM	Bone marrow			pTriplEx2
L3815	MDS	Bone marrow			pTriplEx2
L3816	HEMBA1	whole embryo, mainly head			pME18SFL3
L3817	HEMBB1	whole embryo, mainly body			pME18SFL3
L3823	NT2RM1		NT2		pUC19FL3
L3826	NT2RP1		NT2		pUC19FL3
L3827	NT2RP2		NT2		pME18SFL3
L3828	NT2RP3		NT2		pME18SFL3
L3829	NT2RP4		NT2		pME18SFL3
L3831	OVARC1	ovary, tumor tissue			pME18SFL3

L3832	PLACE1	placenta				pME18SFL3
L3833	PLACE2	placenta				pME18SFL3
L3872	NCI_CGAP_Skn1		skin, normal, 4 pooled sa			pCMV-SPORT6
L3904	NCI_CGAP_Brn64	glioblastoma with EGFR amplification	brain			pCMV-SPORT6
L3905	NCI_CGAP_Brn67	anaplastic oligodendroglioma with 1p/19q loss	brain			pCMV-SPORT6
L4497	NCI_CGAP_Brn22	invasive ductal carcinoma, 3 pooled samples	breast			pCMV-SPORT6
L4501	NCI_CGAP_Sub8					pT7T3D-Pac (Pharmacia) with a modified polylinker
L4556	NCI_CGAP_HN13	squamous cell carcinoma	tongue			pCMV-SPORT6
L4669	NCI_CGAP_Ov41	serous papillary tumor	ovary			pCMV-SPORT6
L4747	NCI_CGAP_Brn41	oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L5565	NCI_CGAP_Brn66	glioblastoma with probably TP53 mutation and witho	brain			pCMV-SPORT6
L5566	NCI_CGAP_Brn70	anaplastic oligodendroglioma	brain			pCMV-SPORT6.cddb
L5569	NCI_CGAP_HN17	normal epithelium	nasopharynx			pAMP10
L5574	NCI_CGAP_HN19	normal epithelium	nasopharynx			pAMP10
L5575	NCI_CGAP_Brn65	glioblastoma without EGFR amplification	brain			pCMV-SPORT6
L5622	NCI_CGAP_Skn3		skin			pCMV-SPORT6
L5623	NCI_CGAP_Skn4	squamous cell carcinoma	skin			pCMV-SPORT6

### Description of Table 5

Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1B.1, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 1B.1, column 8, as determined using the Morbid Map database.

**Table 5**

OMIM Reference	Description
101000	Meningioma, NF2-related, sporadic Schwannoma, sporadic
101000	Neurofibromatosis, type 2
101000	Neurolemmomatosis
101000	Malignant mesothelioma, sporadic
102200	Somatotrophinoma
102772	[AMP deaminase deficiency, erythrocytic]
103600	[Dysalbuminemic hyperthyroxinemia]
103600	[Dysalbuminemic hyperzincemia], 194470
103600	Analbuminemia
103850	Aldolase A deficiency
104150	[AFP deficiency, congenital]
104150	[Hereditary persistence of alpha-fetoprotein]
104500	Amelogenesis imperfecta-2, hypoplastic local type
104770	Amyloidosis, secondary, susceptibility to
106100	Angioedema, hereditary
106210	Peters anomaly
106210	Cataract, congenital, with late-onset corneal dystrophy
106210	Foveal hypoplasia, isolated, 136520
106210	Aniridia
107271	CD59 deficiency
107300	Antithrombin III deficiency
107670	Apolipoprotein A-II deficiency
107776	Colton blood group, 110450
107777	Diabetes insipidus, nephrogenic, autosomal recessive, 222000
108725	Atherosclerosis, susceptibility to
109560	Leukemia/lymphoma, B-cell, 3
110700	Vivax malaria, susceptibility to
112261	Fibrodysplasia ossificans progressiva
114550	Hepatocellular carcinoma
114835	Monocyte carboxyesterase deficiency
115500	Acatalasemia
116800	Cataract, Marner type
116806	Colorectal cancer
116860	Cavernous angiomatic malformations
118485	Polycystic ovary syndrome with hyperandrogenemia



120070	Alport syndrome, autosomal recessive, 203780
120131	Alport syndrome, autosomal recessive, 203780
120131	Hematuria, familial benign
120140	Osteoarthrosis, precocious
120140	SED congenita
120140	SMED Strudwick type
120140	Stickler syndrome, type I
120140	Wagner syndrome, type II
120140	Achondrogenesis-hypochondrogenesis, type II
120140	Kniest dysplasia
120220	Bethlem myopathy, 158810
120240	Bethlem myopathy, 158810
120260	Epiphyseal dysplasia, multiple, type 2, 600204
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C
120700	C3 deficiency
121050	Contractural arachnodactyly, congenital
121360	Myeloid leukemia, acute, M4Eo subtype
123000	Craniometaphyseal dysplasia
123580	Cataract, congenital, autosomal dominant
123620	Cataract, cerulean, type 2, 601547
123940	White sponge nevus, 193900
126060	Anemia, megaloblastic, due to DHFR deficiency
126090	Hyperphenylalaninemia due to pterin-4a-carbinolamine dehydratase deficiency, 264070
126337	Myxoid liposarcoma
126600	Doyne honeycomb retinal dystrophy
126600	Drusen, radial, autosomal dominant
129010	Neuropathy, congenital hypomyelinating, 1
129900	EEC syndrome-1
130500	Elliptocytosis-1
131100	Multiple endocrine neoplasia I
131100	Prolactinoma, hyperparathyroidism, carcinoid syndrome
131100	Carcinoid tumor of lung
131210	Atherosclerosis, susceptibility to
131400	Eosinophilia, familial
133171	[Erythrocytosis, familial], 133100
133200	Erythrokeratoderma variabilis
133780	Vitreoretinopathy, exudative, familial
134570	Factor XIII A deficiency
134790	Hyperferritinemia-cataract syndrome, 600886
135940	Ichthyosis vulgaris, 146700
136132	[Fish-odor syndrome], 602079
136435	Ovarian dysgenesis, hypergonadotropic, with normal karyotype, 233300
136530	Male infertility, familial
136836	Fucosyltransferase-6 deficiency
138030	[Hyperproglucagonemia]
138040	Cortisol resistance
138079	Hyperinsulinism, familial, 602485
138079	MODY, type 2, 125851
138140	Glucose transport defect, blood-brain barrier

138760	[Glyoxalase II deficiency]
138981	Pulmonary alveolar proteinosis, 265120
139191	Growth hormone deficient dwarfism
139350	Epidermolytic hyperkeratosis, 113800
139350	Keratoderma, palmoplantar, nonepidermolytic
140100	[Anhaptoglobinemia]
140100	[Hypohaptoglobinemia]
141750	Alpha-thalassemia/mental retardation syndrome, type 1
141800	Methemoglobinemias, alpha-
141800	Thalassemias, alpha-
141800	Erythremias, alpha-
141800	Heinz body anemias, alpha-
141850	Thalassemia, alpha-
141850	Erythrocytosis
141850	Heinz body anemia
141850	Hemoglobin H disease
141850	Hypochromic microcytic anemia
142600	Hemolytic anemia due to hexokinase deficiency
143200	Wagner syndrome
143200	Erosive vitreoretinopathy
143890	Hypercholesterolemia, familial
145001	Hyperparathyroidism-jaw tumor syndrome
145981	Hypocalciuric hypercalcemia, type II
146760	[IgG receptor I, phagocytic, familial deficiency of]
146790	Lupus nephritis, susceptibility to
147050	Atopy
147141	Leukemia, acute lymphoblastic
147670	Rabson-Mendenhall syndrome
147670	Diabetes mellitus, insulin-resistant, with acanthosis nigricans
147670	Leprechaunism
147781	Atopy, susceptibility to
148040	Epidermolysis bullosa simplex, Koebner, Dowling-Meara, and Weber-Cockayne types, 131900, 131760, 131800
148041	Pachyonychia congenita, Jadassohn-Lewandowsky type, 167200
148043	Meesmann corneal dystrophy, 122100
148070	Liver disease, susceptibility to, from hepatotoxins or viruses
148370	Keratolytic winter erythema
148900	Klippel-Feil syndrome with laryngeal malformation
151385	Leukemia, acute myeloid
151390	Leukemia, acute T-cell
151410	Leukemia, chronic myeloid
151440	Leukemia, T-cell acute lymphoblastoid
151670	Hepatic lipase deficiency
152445	Vohwinkel syndrome, 124500
152445	Erythrokeratoderma, progressive symmetric, 602036
152780	Hypogonadism, hypergonadotropic
152780	Male pseudohermaphroditism due to defective LH
153455	Cutis laxa, recessive, type I, 219100
153700	Macular dystrophy, vitelliform type
154276	Malignant hyperthermia susceptibility 3
154545	Chronic infections, due to opsonin defect
155555	[Red hair/fair skin]

155555	UV-induced skin damage, vulnerability to
156850	Cataract, congenital, with microphthalmia
159000	Muscular dystrophy, limb-girdle, type 1A
159001	Muscular dystrophy, limb-girdle, type 1B
160980	Carney myxoma-endocrine complex
161015	Mitochondrial complex I deficiency, 252010
164009	Leukemia, acute promyelocytic, NUMA/RARA type
164500	Spinocerebellar ataxia-7
164731	Ovarian carcinoma, 167000
164920	Piebaldism
164920	Mast cell leukemia
164920	Mastocytosis with associated hematologic disorder
164953	Liposarcoma
165240	Pallister-Hall syndrome, 146510
165240	Postaxial polydactyly type A1, 174200
165240	Greig cephalopolysyndactyly syndrome, 175700
168461	Multiple myeloma, 254250
168461	Parathyroid adenomatosis 1
168461	Centrocytic lymphoma
168468	Metaphyseal chondrodysplasia, Murk Jansen type, 156400
170650	Periodontitis, juvenile
171860	Hemolytic anemia due to phosphofructokinase deficiency
172400	Hemolytic anemia due to glucosephosphate isomerase deficiency
172400	Hydrops fetalis, one form
172471	Glycogenosis, hepatic, autosomal
173610	Platelet alpha/delta storage pool deficiency
174000	Medullary cystic kidney disease, AD
174810	Osteolysis, familial expansile
176640	Creutzfeldt-Jakob disease, 123400
176640	Gerstmann-Straussler disease, 137440
176640	Insomnia, fatal familial
176880	Protein S deficiency
178300	Ptois, hereditary congenital, 1
178640	Pulmonary alveolar proteinosis, congenital, 265120
179095	Male infertility
179615	Reticulosis, familial histiocytic, 267700
179615	Severe combined immunodeficiency, B cell-negative, 601457
179616	Severe combined immunodeficiency, B cell-negative, 601457
179755	Renal cell carcinoma, papillary, 1
180104	Retinitis pigmentosa-9
180105	Retinitis pigmentosa-10
180200	Osteosarcoma, 259500
180200	Pinealoma with bilateral retinoblastoma
180200	Retinoblastoma
180200	Bladder cancer, 109800
180385	Leukemia, acute T-cell
180721	Retinitis pigmentosa, digenic
180840	Susceptibility to IDDM
180901	Malignant hyperthermia susceptibility 1, 145600
180901	Central core disease, 117000
181405	Scapuloperoneal spinal muscular atrophy, New England type
181460	Schistosoma mansoni, susceptibility/resistance to

181510	Schizophrenia
182280	Small-cell cancer of lung
182381	Renal glucosuria, 253100
182860	Pyropoikilocytosis
182860	Spherocytosis, recessive
182860	Elliptocytosis-2
186580	Arthrocutaneous uveitis
188070	Bleeding disorder due to defective thromboxane A2 receptor
188826	Sorsby fundus dystrophy, 136900
189800	Preeclampsia/eclampsia
190685	Down syndrome
191092	Tuberous sclerosis-2
191181	Cervical carcinoma
191315	Insensitivity to pain, congenital, with anhidrosis, 256800
192090	Ovarian carcinoma
192090	Breast cancer, lobular
192090	Endometrial carcinoma
192090	Gastric cancer, familial, 137215
192974	Neonatal alloimmune thrombocytopenia
192974	Glycoprotein Ia deficiency
193235	Vitreoretinopathy, neovascular inflammatory
193300	Renal cell carcinoma
193300	von Hippel-Lindau syndrome
194070	Wilms tumor, type 1
194070	Denys-Drash syndrome
194070	Frasier syndrome, 136680
203740	Alpha-ketoglutarate dehydrogenase deficiency
205900	Anemia, Diamond-Blackfan
208400	Aspartylglucosaminuria
209901	Bardet-Biedl syndrome 1
212138	Carnitine-acylcarnitine translocase deficiency
216550	Cohen syndrome
216900	Achromatopsia
217800	Macular corneal dystrophy
218030	Apparent mineralocorticoid excess, hypertension due to
219800	Cystinosis, nephropathic
221770	Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy
222745	DECR deficiency
222800	Hemolytic anemia due to bisphosphoglycerate mutase deficiency
222900	Sucrose intolerance
227646	Fanconi anemia, type D
227650	Fanconi anemia, type A
230800	Gaucher disease
230800	Gaucher disease with cardiovascular calcification
231550	Achalasia-addisonianism-alacrimia syndrome
231670	Glutaricaciduria, type I
231675	Glutaricaciduria, type IIC
231680	Glutaricaciduria, type IIA
232500	Glycogen storage disease IV
232600	McArdle disease
233700	Chronic granulomatous disease due to deficiency of NCF-1

236100	Holoprosencephaly-1
236200	Homocystinuria, B6-responsive and nonresponsive types
236700	McKusick-Kaufman syndrome
240300	Autoimmune polyglandular disease, type I
245349	Lacticacidemia due to PDX1 deficiency
245900	Norum disease
245900	Fish-eye disease
248600	Maple syrup urine disease, type Ia
249100	Familial Mediterranean fever
250850	Hypermethioninemia, persistent, autosomal dominant, due to methionine adenosyltransferase I/III deficiency
253000	Mucopolysaccharidosis IVA
253200	Maroteaux-Lamy syndrome, several forms
259700	Osteopetrosis, recessive
259770	Osteoporosis-pseudoglioma syndrome
259900	Hyperoxaluria, primary, type 1
261670	Myopathy due to phosphoglycerate mutase deficiency
266200	Anemia, hemolytic, due to PK deficiency
266600	Inflammatory bowel disease-1
267750	Knobloch syndrome
268800	Sandhoff disease, infantile, juvenile, and adult forms
268800	Spinal muscular atrophy, HEXB-related
272800	Tay-Sachs disease
272800	[Hex A pseudodeficiency]
272800	GM2-gangliosidosis, juvenile, adult
274180	Thromboxane synthase deficiency
276600	Tyrosinemia, type II
276700	Tyrosinemia, type I
300011	Menkes disease, 309400
300011	Occipital horn syndrome, 304150
300011	Cutis laxa, neonatal
300046	Mental retardation, X-linked 23, nonspecific
300047	Mental retardation, X-linked 20
300067	Subcortical laminar heterotopia, X-linked dominant
300067	Lissencephaly, X-linked
300071	Night blindness, congenital stationary, type 2
300075	Coffin-Lowry syndrome, 303600
300077	Mental retardation, X-linked 29
300110	Night blindness, congenital stationary, X-linked incomplete, 300071
300121	Subcortical laminar heterotopia, X-linked, 300067
300121	Lissencephaly, X-linked, 300067
300127	Mental retardation, X-linked, 60
300600	Ocular albinism, Forsius-Eriksson type
301000	Thrombocytopenia, X-linked, 313900
301000	Wiskott-Aldrich syndrome
301200	Amelogenesis imperfecta
301201	Amelogenesis imperfecta-3, hypoplastic type
301830	Arthrogryposis, X-linked (spinal muscular atrophy, infantile, X-linked)
301835	Arts syndrome
302350	Nance-Horan syndrome
302801	Charcot-Marie-Tooth neuropathy, X-linked-2, recessive
305435	Heterocellular hereditary persistence of fetal hemoglobin, Swiss type

305450	FG syndrome
306000	Glycogenosis, X-linked hepatic, type I
306000	Glycogenosis, X-linked hepatic, type II
307800	Hypophosphatemia, hereditary
308800	Keratosis follicularis spinulosa decalvans
309470	Mental retardation, X-linked, syndromic-3, with spastic diplegia
309500	Renpenning syndrome-1
309510	Mental retardation, X-linked, syndromic-1, with dystonic movements, ataxia, and seizures
309605	Mental retardation, X-linked, syndromic-4, with congenital contractures and low fingertip arches
309610	Mental retardation, X-linked, syndromic-2, with dysmorphism and cerebral atrophy
309850	Brunner syndrome
311050	Optic atrophy, X-linked
311200	Oral-facial-digital syndrome 1
311850	Phosphoribosyl pyrophosphate synthetase-related gout
312040	N syndrome, 310465
312060	Properdin deficiency, X-linked
312170	Pyruvate dehydrogenase deficiency
312700	Retinoschisis
313400	Spondyloepiphyseal dysplasia tarda
313700	Perineal hypospadias
313700	Prostate cancer
313700	Spinal and bulbar muscular atrophy of Kennedy, 313200
313700	Breast cancer, male, with Reifenstein syndrome
313700	Androgen insensitivity, several forms
314580	Wieacker-Wolff syndrome
600040	Colorectal cancer
600045	Xeroderma pigmentosum, group E, subtype 2
600065	Leukocyte adhesion deficiency, 116920
600079	Colon cancer
600140	Rubenstein-Taybi syndrome, 180849
600151	Bardet-Biedl syndrome 3
600163	Long QT syndrome-3
600194	Ichthyosis bullosa of Siemens, 146800
600223	Spinocerebellar ataxia-4
600231	Palmoplantar keratoderma, Bothnia type
600234	HMG-CoA synthase-2 deficiency
600273	Polycystic kidney disease, infantile severe, with tuberous sclerosis
600276	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy, 125310
600319	Diabetes mellitus, insulin-dependent, 4
600354	Spinal muscular atrophy-1, 253300
600354	Spinal muscular atrophy-2, 253550
600354	Spinal muscular atrophy-3, 253400
600374	Bardet-Biedl syndrome 4
600528	CPT deficiency, hepatic, type I, 255120
600536	Myopathy, congenital
600631	Enuresis, nocturnal, 1
600652	Deafness, autosomal dominant 4
600678	Cancer susceptibility

600757	Orofacial cleft-3
600760	Pseudohypoaldosteronism, type I, 264350
600760	Liddle syndrome, 177200
600761	Pseudohypoaldosteronism, type I, 264350
600761	Liddle syndrome, 177200
600795	Dementia, familial, nonspecific
600807	Bronchial asthma
600808	Enuresis, nocturnal, 2
600850	Schizophrenia disorder-4
600882	Charcot-Marie-Tooth neuropathy-2B
600887	Endometrial carcinoma
600897	Cataract, zonular pulverulent-1, 116200
600900	Muscular dystrophy, limb-girdle, type 2E
600918	Cystinuria, type III
600956	Persistent Mullerian duct syndrome, type II, 261550
600957	Persistent Mullerian duct syndrome, type I, 261550
600975	Glaucoma 3, primary infantile, B
601072	Deafness, autosomal recessive 8
601090	Iridogoniodysgenesis, 601631
601105	Pycnodysostosis, 265800
601145	Epilepsy, progressive myoclonic 1, 254800
601238	Cerebellar ataxia, Cayman type
601284	Hereditary hemorrhagic telangiectasia-2, 600376
601313	Polycystic kidney disease, adult type I, 173900
601362	DiGeorge syndrome/velocardiofacial syndrome complex-2
601386	Deafness, autosomal recessive 12
601412	Deafness, autosomal dominant 7
601472	Charcot-Marie-Tooth neuropathy-2D
601493	Cardiomyopathy, dilated 1C
601567	Combined factor V and VIII deficiency, 227300
601596	Charcot-Marie-Tooth neuropathy, demyelinating
601649	Blepharophimosis, epicanthus inversus, and ptosis, type 2
601650	Paraganglioma, familial nonchromaffin, 2
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750
601669	Hirschsprung disease, one form
601692	Reis-Bucklers corneal dystrophy
601692	Corneal dystrophy, Avellino type
601692	Corneal dystrophy, Groenouw type I, 121900
601692	Corneal dystrophy, lattice type I, 122200
601769	Osteoporosis, involutional
601769	Rickets, vitamin D-resistant, 277440
601780	Ceroid-lipofuscinosis, neuronal-6, variant late infantile
601785	Carbohydrate-deficient glycoprotein syndrome, type I, 212065
601843	Hypothyroidism, congenital, 274400
601846	Muscular dystrophy with rimmed vacuoles
601863	Bare lymphocyte syndrome, complementation group C
601884	[High bone mass]
601920	Alagille syndrome, 118450
601928	Monilethrix, 158000
602028	Multiple myeloma
602078	Fibrosis of extraocular muscles, congenital, 2
602080	Paget disease of bone-2

602089	Hemangioma, capillary, hereditary
602092	Deafness, autosomal recessive 18
602094	Lipodystrophy, familial partial
602116	Glioma
602121	Deafness, autosomal dominant nonsyndromic sensorineural, 1, 124900
602136	Refsum disease, infantile, 266510
602136	Zellweger syndrome-1, 214100
602136	Adrenoleukodystrophy, neonatal, 202370
602153	Monilethrix, 158000
602216	Peutz-Jeghers syndrome, 175200
602447	Coronary artery disease, susceptibility to
602460	Deafness, autosomal dominant 15, 602459
602477	Febrile convulsions, familial, 2
602491	Hyperlipidemia, familial combined, 1
602568	Homocystinuria-megaloblastic anemia, cbl E type, 236270
602716	Nephrosis-1, congenital, Finnish type, 256300
602783	Spastic paraplegia-7

#### *Mature Polypeptides*

The present invention also encompasses mature forms of a polypeptide having the amino acid sequence of SEQ ID NO:Y and/or the amino acid sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional activities of the full-length or mature form of the polypeptide (e.g., biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species



of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra*.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1A.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the predicted mature form of the polypeptide as delineated in columns 14 and 15 of Table 1A. Moreover, fragments or variants of these polypeptides (such as, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide that hybridizes under stringent conditions to the complementary strand of the polynucleotide encoding these polypeptides) are also encompassed by the invention. In preferred embodiments, these fragments or variants retain one or more functional activities of the full-length or mature form of the polypeptide (e.g., biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention). Antibodies that bind the polypeptides of the invention, and polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotides encoding proteins comprising, or consisting of, the predicted mature form of polypeptides of the invention (e.g., polynucleotides having the sequence of SEQ ID NO: X (Table 1A, column 4), the sequence delineated in columns 7 and 8 of Table 1A, and a sequence

encoding the mature polypeptide delineated in columns 14 and 15 of Table 1A (e.g., the sequence of SEQ ID NO:X encoding the mature polypeptide delineated in columns 14 and 15 of Table 1)) are also encompassed by the invention, as are fragments or variants of these polynucleotides (such as, fragments as described herein, polynucleotides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polynucleotides, and nucleic acids which hybridizes under stringent conditions to the complementary strand of the polynucleotide).

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 15 residues of the predicted cleavage point (i.e., having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 more or less contiguous residues of SEQ ID NO:Y at the N-terminus when compared to the predicted mature form of the polypeptide (e.g., the mature polypeptide delineated in columns 14 and 15 of Table 1). Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as described below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

#### *Polynucleotide and Polypeptide Variants*

The present invention is also directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X that encodes the polypeptide sequence as defined in columns 13 and 14 of Table 1A, nucleotide sequences encoding the polypeptide sequence as defined in columns 13 and 14 of Table 1A, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in Table 1B, nucleotide sequences encoding the polypeptide as defined in Table 1B, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1C, nucleotide sequences encoding the polypeptide encoded by the

nucleotide sequence as defined in column 6 of Table 1C, the cDNA sequence contained in ATCC Deposit No:Z, nucleotide sequences encoding the polypeptide encoded by the cDNA sequence contained in ATCC Deposit No:Z, and/or nucleotide sequences encoding a mature (secreted) polypeptide encoded by the cDNA sequence contained in ATCC Deposit No:Z.

5           The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, the polypeptide as defined in columns 13 and 14 of Table 1A, the polypeptide sequence as defined in Table 1B, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as  
10 defined in column 6 of Table 1C, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, the polypeptide sequence encoded by the cDNA sequence contained in ATCC Deposit No:Z and/or a mature (secreted) polypeptide encoded by the cDNA sequence contained in ATCC Deposit No:Z.

15           "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

          Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected  
20 from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of ATCC Deposit No:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in ATCC Deposit No:Z which encodes the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA in ATCC Deposit No:Z which encodes a  
25 mature polypeptide (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)); (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of ATCC Deposit No:Z, which encodes a biologically active fragment of a polypeptide; (e) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of ATCC Deposit No:Z, which encodes an antigenic fragment of a polypeptide; (f) a nucleotide sequence encoding a polypeptide comprising the complete amino  
30 acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (g) a nucleotide sequence encoding a mature polypeptide of the amino acid sequence of SEQ ID NO:Y (i.e., a secreted polypeptide (e.g., as delineated in columns 14 and 15 of Table 1A)) or a mature polypeptide of the amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (h) a nucleotide sequence encoding a biologically active fragment of a polypeptide  
35 having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (i) a nucleotide sequence encoding an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the

complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), or (j) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in Table 1B or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in Table 1B or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group

consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; (b) the amino acid sequence of a mature (secreted) form of a polypeptide having the amino acid sequence of SEQ ID NO:Y (e.g., as delineated in columns 14 and 15 of Table 1A) or a mature form of the amino acid sequence encoded by the cDNA in ATCC Deposit No:Z mature; (c) the amino acid sequence of a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z; and (d) the amino acid sequence of an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in ATCC Deposit No:Z.

The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in ATCC Deposit No:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C, the amino acid sequence as defined in Table 1B, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1B or 2 as the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the

present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., the amino acid sequence delineated in columns 14 and 15) or a fragment thereof, Table 1B.1 (e.g., the amino acid sequence identified in column 6) or a fragment thereof, Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1C or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence of the polypeptide encoded by cDNA contained in ATCC Deposit No:Z, or a fragment thereof, the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in ATCC Deposit No:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and

C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II,



Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

5           Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (J. Biol. Chem. 268: 2984-2988 (1993)) reported variant KGF proteins  
10   having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

          Moreover, ample evidence demonstrates that variants often retain a biological activity  
15   similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the  
20   molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

          Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other  
25   biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and  
30   otherwise known in the art.

          Thus, the invention further includes polypeptide variants which show a biological or functional activity of the polypeptides of the invention (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus). Such variants include deletions, insertions, inversions, repeats, and substitutions selected  
35   according to general rules known in the art so as have little effect on activity.

          The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g.,

encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues).

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein and/or a mature (secreted) protein of the invention. Such functional activities include, but are not limited to, biological activity (such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus), antigenicity (ability to bind, or compete with a polypeptide of the invention for binding, to an anti-polypeptide of the invention antibody), immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with a full-length polypeptide of the present invention for binding to an anti-polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In

another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

5 In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological  
10 correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either  
15 *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic  
20 acid sequence of the cDNA contained in ATCC Deposit No:Z, the nucleic acid sequence referred to in Table 1B (SEQ ID NO:X), the nucleic acid sequence disclosed in Table 1A (e.g., the nucleic acid sequence delineated in columns 7 and 8), the nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these  
25 nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to  
30 significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors  
35 indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, *Science* 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment thereof, or leader or secretory sequence, or a sequence facilitating purification, or (v) fusion of the polypeptide with another compound, such as albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved

characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

5 A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a  
10 polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which, for example, comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, the amino acid sequence of the mature (e.g., secreted) polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an amino acid sequence  
15 encoded by the complement of SEQ ID NO:X, an amino acid sequence encoded by cDNA contained in ATCC Deposit No:Z, and/or the amino acid sequence of a mature (secreted) polypeptide encoded by cDNA contained in ATCC Deposit No:Z, or a fragment thereof, which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

20 In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein); (b) the amino acid sequence encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof;  
25 (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in ATCC Deposit No:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid  
30 substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

#### *Polynucleotide and Polypeptide Fragments*

35 The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto; is a

portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the mature (secreted) polypeptide encoded by the cDNA contained in ATCC Deposit No:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the mature amino acid sequence as defined in columns 14 and 15 of Table 1A or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1C or the complementary strand thereto.

The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in ATCC Deposit No:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length ) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100,

3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity; such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

Further representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300,

6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in ATCC Deposit No:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1C column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1C. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1C, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1C, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1C, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1C, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1C, column 2) or fragments or variants thereof. Polypeptides



encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

5 In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1C which correspond to the same ATCC Deposit No:Z (see Table 1C, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

10 In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1C, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A, 1B, or 1C) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

15 In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

25 In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous 30 Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and 35 variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1C are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1C is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1C, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of the amino acid sequence contained in SEQ ID NO:Y, is a portion of the mature form of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, is a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, is a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, is a portion of the amino acid sequence of a mature (secreted) polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or is a portion of an amino acid sequence encoded by the cDNA contained in ATCC Deposit No:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-

120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of cDNA and SEQ ID NO: Y. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities; such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or a mature polypeptide encoded by the cDNA contained in ATCC Deposit No:Z). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C, a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or a mature polypeptide encoded by the cDNA contained in ATCC Deposit No:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g.,

including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y, the mature (secreted) portion of SEQ ID NO:Y as defined in columns 14 and 15 of Table 1A, and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in ATCC Deposit No:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) may still be retained. For example the ability of the shortened mutin to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutin with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in ATCC Deposit No:Z, or the polynucleotide sequence as defined in column 6 of Table 1C, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in ATCC Deposit No:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity such as, for example, activity useful in detecting, preventing, diagnosing, prognosticating, treating, and/or ameliorating diabetes mellitus; ability to multimerize; ability to bind a ligand; antigenic ability useful for production of polypeptide specific antibodies) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

### *Epitopes and Antibodies*

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1C or the complement thereto; the polypeptide sequence encoded by the cDNA contained in ATCC Deposit No:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in ATCC Deposit No:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55,

60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in Table 1B. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNASTar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in Table 1B, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in Table 1B.

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al.,



*supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

Such fusion proteins as those described above may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

#### *Fusion Proteins*

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)).

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as

"DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opin. Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

#### Recombinant and Synthetic Production of Polypeptides of the Invention

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably

include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control

regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

Polypeptides of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant

techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1,

pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

5 In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

10 In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control  
15 regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each  
20 of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of  
25 a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid,  
30 ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

35 The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation,



phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH<sub>4</sub>; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (<sup>121</sup>I, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I), carbon (<sup>14</sup>C), sulfur (<sup>35</sup>S), tritium (<sup>3</sup>H), indium (<sup>111</sup>In, <sup>112</sup>In, <sup>113m</sup>In, <sup>115m</sup>In), technetium (<sup>99</sup>Tc, <sup>99m</sup>Tc), thallium (<sup>201</sup>Tl), gallium (<sup>68</sup>Ga, <sup>67</sup>Ga), palladium (<sup>103</sup>Pd), molybdenum (<sup>99</sup>Mo), xenon (<sup>133</sup>Xe), fluorine (<sup>18</sup>F), <sup>153</sup>Sm, <sup>177</sup>Lu, <sup>159</sup>Gd, <sup>149</sup>Pm, <sup>140</sup>La, <sup>175</sup>Yb, <sup>166</sup>Ho, <sup>90</sup>Y, <sup>47</sup>Sc, <sup>186</sup>Re, <sup>188</sup>Re, <sup>142</sup>Pr, <sup>105</sup>Rh, and <sup>97</sup>Ru.

In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, <sup>177</sup>Lu, <sup>90</sup>Y, <sup>166</sup>Ho, and <sup>153</sup>Sm, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is <sup>111</sup>In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is <sup>90</sup>Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

As mentioned, the proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are

well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000,

25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*,  
5 *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There  
10 are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to  
15 which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at  
20 an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or  
25 more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of  
30 polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of  
35 the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine

versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in ATCC Deposit No:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus,

in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in ATCC Deposit No:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in

solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially  
5 form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between  
10 Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in  
15 the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine  
20 residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US  
25 Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering  
30 techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the  
35 invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent

Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

### Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for



one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include the predicted epitopes shown in Table 1B, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less

than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

5           The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

10           Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and  
15           ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for  
20           example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

          The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex,  
25           and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as  
30           receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication  
35           WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998);

Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all  
5 incorporated by reference herein in their entirety).

Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological  
10 samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically  
15 conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the  
20 disclosures of which are incorporated herein by reference in their entirety.

The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by  
25 glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants  
35 may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides,

oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of *Current Protocols in Immunology*, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor

tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

5 In general, the sample containing human B cells is inoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal.  
10 However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g.,  
15 SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g., SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

20 Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

25 For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine).  
30 Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display  
35 methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene

187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol. Methods* 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting

(EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein Engineering* 7(6):805-814 (1994); Roguska. et al., *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

5 Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 10 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be 15 introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody 20 production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using 25 conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed 30 discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in 35 their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:595-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

#### *Polynucleotides Encoding Antibodies*

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded



by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties ), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al.,

J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038-1041 (1988)).

#### *Methods of Producing Antibodies*

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of

the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention *in situ*. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous

translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., *Methods in Enzymol.* 153:51-544 (1987)).

5 In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products.

10 Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, breast

15 cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be

20 transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably

25 integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

30 A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., *Cell* 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA* 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:817 (1980)) genes can be employed in tk-, hgp<sup>r</sup>t- or ap<sup>r</sup>t- cells, respectively. Also, antimetabolite resistance can be used as the basis of

35 selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., *Natl. Acad. Sci. USA* 77:357 (1980); O'Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA*

78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used

which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA

and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341 (1992) (said references incorporated by reference in their entireties).

As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; and Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example,



monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an

apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

### *Immunophenotyping*

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the gene of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid

matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

#### *Assays For Antibody Binding*

The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a

membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

Antibodies of the invention may be characterized using immunocytochemistry methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the

expression of an antigen or with vector alone using techniques commonly known in the art. Antibodies that bind antigen transfected cells, but not vector-only transfected cells, are antigen specific.

5                    *Therapeutic Uses*

Table 1D also provides information regarding biological activities and preferred therapeutic uses (i.e. see, "Preferred Indications" column) for polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof). Table 1D also provides information regarding assays which may be used to test polynucleotides and polypeptides of the invention (including antibodies, agonists, and/or antagonists thereof) for the corresponding biological activities. The first column ("Gene No.") provides the gene number in the application for each clone identifier. The second column ("cDNA ATCC Deposit No:Z") provides the unique clone identifier for each clone as previously described and indicated in Table 1A, Table 1B, and Table 1C. The third column ("AA SEQ ID NO:Y") indicates the Sequence Listing SEQ ID Number for polypeptide sequences encoded by the corresponding cDNA clones (also as indicated in Table 1A, Table 1B, and Table 2). The fourth column ("Biological Activity") indicates a biological activity corresponding to the indicated polypeptides (or polynucleotides encoding said polypeptides). The fifth column ("Exemplary Activity Assay") further describes the corresponding biological activity and also provides information pertaining to the various types of assays which may be performed to test, demonstrate, or quantify the corresponding biological activity.

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, diabetes mellitus. The treatment and/or prevention of diabetes mellitus associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with diabetes mellitus. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a

mammal, and most preferably a human, patient for treating diabetes mellitus. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a polypeptide of the invention (such as, for example, a predicted linear epitope shown in Table 1B; or a conformational epitope, including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to detect, diagnose, prevent, treat, prognosticate, and/or ameliorate diabetes mellitus or conditions associated with aberrant expression and/or activity of a polypeptide of the invention. The treatment and/or prevention of diabetes mellitus or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diabetes mellitus related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include

those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

5

### *Gene Therapy*

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a diabetes mellitus associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in

which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and



muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem

or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

5 In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and  
10 Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that  
15 expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

#### *Demonstration of Therapeutic or Prophylactic Activity*

The compounds or pharmaceutical compositions of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in  
20 humans. For example, *in vitro* assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, *in vitro* assays which can be used to determine whether administration of a specific compound is  
25 indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

#### *Therapeutic/Prophylactic Administration and Composition*

30 The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that  
35 limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

5 Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules; recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, 10 intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the 15 pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

20 In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, 25 non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in 30 the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et 35 al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance,

Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium

stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced

by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

### *Diagnosis and Imaging*

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, prognosticate, or monitor diabetes mellitus and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing diabetes mellitus, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of diabetes mellitus. With respect to insulin resistance, the presence of a relatively high or low amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of insulin resistance into diabetes mellitus.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H),

indium (<sup>112</sup>In), and technetium (<sup>99</sup>Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another  
5 embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

#### *Kits*

10 The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control  
15 antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a  
20 detectable substrate).

In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide  
25 antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The  
30 polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

35 In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or



polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

#### Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1B.1, column 8 provides the chromosome location of some of the polynucleotides of the invention.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1B and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man

(available on line through Johns Hopkins University Welch Medical Library)). Column 9 of Table 1B.1 provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1B.1, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA  
5 precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined  
10 in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified,  
15 this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents  
20 encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Diseases").

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in  
25 cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the  
30 polynucleotide of the invention, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.  
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Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, metabolic disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254, 1497 (1991); and Egholm et al., Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., *supra*) Indeed, the human

counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., *supra*)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, and/or prognosis of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to

correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods", and Examples 16, 17 and 18).

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992)). Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to those shown in Table 1B. Panels of such reagents can identify tissue by species and/or by organ type. In a similar

fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, those disclosed in Table 1B, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

#### Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein



gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Ti}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ , ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Ti}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or

double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, <sup>213</sup>Bi, or other radioisotopes such as, for example, <sup>103</sup>Pd, <sup>133</sup>Xe, <sup>131</sup>I, <sup>68</sup>Ge, <sup>57</sup>Co, <sup>65</sup>Zn, <sup>85</sup>Sr, <sup>32</sup>P, <sup>35</sup>S, <sup>90</sup>Y, <sup>153</sup>Sm, <sup>153</sup>Gd, <sup>169</sup>Yb, <sup>51</sup>Cr, <sup>54</sup>Mn, <sup>75</sup>Se, <sup>113</sup>Sn, <sup>90</sup>Yttrium, <sup>117</sup>Tin, <sup>186</sup>Rhenium, <sup>166</sup>Holmium, and <sup>188</sup>Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope <sup>90</sup>Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope <sup>111</sup>In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope <sup>131</sup>I.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect

to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. 'A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

### ***Diagnostic Assays***

The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those related to biological activities described in Table 1D and, also as described herein under the section heading "Biological Activities".

For a number of disorders, substantially altered (increased or decreased) levels of gene

expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during  
5 diagnosis of a disorder, which involves measuring the expression level of the gene encoding the polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue  
10 or autopsy tissue.

The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or  
15 prognosticate diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

By "assaying the expression level of the gene encoding the polypeptide" is intended  
20 qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample  
25 is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual,  
30 cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body  
35 fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

Total cellular RNA can be isolated from a biological sample using any suitable

technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, *Anal. Biochem.* 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of polypeptides of the invention compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

Assaying polypeptide levels in a biological sample can occur using antibody-based techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., *J. Cell. Biol.* 101:976-985 (1985); Jalkanen, M., et al., *J. Cell. Biol.* 105:3087-3096 (1987)). Other antibody-based methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of interest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by

immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

5 In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the polypeptides of the invention (shown in Table 1B) may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

10 In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a polypeptide of the invention may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

15 The antibodies (or fragments thereof), and/or polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The antibody (or fragment thereof) or polypeptide is preferably applied by  
20 overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the gene product, or conserved variants or peptide fragments, or polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide  
25 variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

Immunoassays and non-immunoassays for gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture,  
30 in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of  
35 immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled antibody or detectable polypeptide of the invention. The solid phase support may then be washed with the buffer a

second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

The binding activity of a given lot of antibody or antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

In addition to assaying polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, polypeptides and/or antibodies of the invention are used to image diseased cells, such as neoplasms. In another embodiment, polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of an mRNA) and/or antibodies (e.g., antibodies directed to any one or a combination of the epitopes of a polypeptide of the invention, antibodies directed to a conformational epitope of a polypeptide of the invention, or antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells.

Antibody labels or markers for *in vivo* imaging of polypeptides of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP

171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne *et al.*, *Nature* 312:643 (1984); Neuberger *et al.*, *Nature* 314:268 (1985).

Additionally, any polypeptides of the invention whose presence can be detected, can be administered. For example, polypeptides of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, <sup>131</sup>I, <sup>112</sup>In, <sup>99m</sup>Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the antigenic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

With respect to antibodies, one of the ways in which an antibody of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL.; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.



Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect polypeptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

The antibody can also be detectably labeled using fluorescence emitting metals such as  $^{152}\text{Eu}$ , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

#### Methods for Detecting Diseases

In general, a disease may be detected in a patient based on the presence of one or more proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a disease or disorder, including cancer and/or as described elsewhere herein. In addition, such proteins may be useful for the detection of other diseases and cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding polypeptides of the invention, which is also indicative of the presence or absence of a disease or disorder, including

cancer. In general, polypeptides of the invention should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In  
5 general, the presence or absence of a disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of a binding agent(s)  
10 immobilized on a solid support to bind to and remove the polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an  
15 anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable  
20 polypeptides for use within such assays include polypeptides of the invention and portions thereof, or antibodies, to which the binding agent binds, as described above.

The solid support may be any material known to those of skill in the art to which polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be  
25 a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the  
30 term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of  
35 time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and

preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

#### Gene Therapy Methods

Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldgrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like.

5 However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

10 The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

15 Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the  
20 ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

25 Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart,  
30 lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is  
35 similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells.

They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

5 For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of  
10 nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous  
15 membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in  
20 the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome  
25 preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987)  
30 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example,  
35 N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein

incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein  
5 incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

10 Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG),  
15 dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of  
20 cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is  
25 circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles  
30 (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the  
35 material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic

lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979)); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ratio will be from about 5:1 to about 1:5. More preferably, the ratio will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and  $\text{CaPO}_4$  precipitation. In one alternative, the retroviral

plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al. Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells.



Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

5 For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are  
10 infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in*  
15 *vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24,  
20 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra et al., *Nature* 342:435-438 (1989), which are herein incorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than  
25 desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the  
30 endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the  
35 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction

site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

5 The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

10 The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

15 The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

20 Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

30 A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

35 Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

### **Biological Activities**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

Members of the secreted family of proteins are believed to be involved in biological activities associated with, for example, cellular signaling. Accordingly, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments

and variants thereof) may be used in diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders associated with aberrant activity of secreted polypeptides.

In preferred embodiments, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, prognosis, prevention, treatment, and/or amelioration of diseases and/or disorders relating to diabetes mellitus and/or a condition associated with diabetes mellitus (e.g., hyperglycemia, obesity, diabetic retinopathy, mononeuropathy, polyneuropathy, atherosclerosis, ulcers, heart disease, anemia, stroke, gangrene (e.g., of the feet and hands), impotence, infection, cataract, poor kidney function, malfunctioning of the autonomic nervous system, impaired white blood cell function, Carpal tunnel syndrome, Dupuytren's contracture, diabetic ketoacidosis, and as described in "Renal Disorders", "Wound Healing and Epithelial Cell Proliferation", "Endocrine Disorders", "Reproductive System Disorders", and "Gastrointestinal Disorders" sections below).

In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognosticate diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

Thus, polynucleotides, translation products and antibodies of the invention are useful in the diagnosis, detection, prevention, prognostication, and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, prohormone activation, neurotransmitter activity, cellular signaling, cellular proliferation, cellular differentiation, and cell migration.

More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, treatment and/or amelioration of diseases and/or disorders associated with the following system or systems.

#### **Renal Disorders**

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate disorders of the renal system. Renal disorders which can be detected, prevented, diagnosed, prognosticated, treated, and/or ameliorated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

Kidney diseases which can be detected, prevented, diagnosed, prognosticated, treated, and/or ameliorated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory

diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting from urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

In addition, compositions of the invention can be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

Compositions of the invention can also be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic,

described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

#### Wound Healing and Epithelial Cell Proliferation

5 In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists  
10 of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and  
15 antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present  
20 invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft,  
25 dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

30 It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II  
35 pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides,

agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the

present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

10 In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

### **Endocrine Disorders**

20 Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: 25 disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or 30 detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders 35 and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes



insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B.2, column 5 (Tissue Distribution Library Code).

### **Reproductive System Disorders**

The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders of the testes; including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases and disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis,

candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, leiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the

present invention may be used in the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosus, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

Other disorders and/or diseases of the female reproductive system that may be detected, prevented, diagnosed, prognosticated, treated, and/or ameliorated by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

#### **Gastrointestinal Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to detect, prevent, diagnose, prognosticate, treat, and/or ameliorate gastrointestinal diseases and disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma)), and ulcers, such as peptic ulcers.

Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular

occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess.).

Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid,

squamous carcinoma, primary lymphoma]], peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus),

tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

### **Chemotaxis**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also

be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

### **Binding Activity**

5 A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

10 Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the  
15 molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe  
20 binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

25 Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

30 Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

35 Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell



responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta,

bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

5           Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

10           Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and  $^3\text{[H]}$  thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of  
15 the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of  $^3\text{[H]}$  thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of  $^3\text{[H]}$  thymidine. Both agonist and antagonist compounds may be identified by this procedure.

20           In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the  
25 ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

30           All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

35           Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has

occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

5

#### **Targeted Delivery**

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

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As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

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In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

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By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubicin, and phenoxyacetamide derivatives of doxorubicin.

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### **Drug Screening**

Further contemplated is the use of the polypeptides of the present invention, or the  
5 polynucleotides encoding these polypeptides, to screen for molecules which modify the activities  
of the polypeptides of the present invention. Such a method would include contacting the  
polypeptide of the present invention with a selected compound(s) suspected of having antagonist  
or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the  
10 polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug  
screening techniques. The polypeptide or fragment employed in such a test may be affixed to a  
solid support, expressed on a cell surface, free in solution, or located intracellularly. One method  
of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with  
recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against  
15 such transformed cells in competitive binding assays. One may measure, for example, the  
formulation of complexes between the agent being tested and a polypeptide of the present  
invention.

Thus, the present invention provides methods of screening for drugs or any other  
agents which affect activities mediated by the polypeptides of the present invention. These  
20 methods comprise contacting such an agent with a polypeptide of the present invention or a  
fragment thereof and assaying for the presence of a complex between the agent and the  
polypeptide or a fragment thereof, by methods well known in the art. In such a competitive  
binding assay, the agents to screen are typically labeled. Following incubation, free agent is  
separated from that present in bound form, and the amount of free or uncomplexed label is a  
25 measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for  
compounds having suitable binding affinity to the polypeptides of the present invention, and is  
described in great detail in European Patent Application 84/03564, published on September 13,  
1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different  
30 small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some  
other surface. The peptide test compounds are reacted with polypeptides of the present invention  
and washed. Bound polypeptides are then detected by methods well known in the art. Purified  
polypeptides are coated directly onto plates for use in the aforementioned drug screening  
techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and  
35 immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which  
neutralizing antibodies capable of binding polypeptides of the present invention specifically

compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

## 5                    **Antisense And Ribozyme (Antagonists)**

          In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA ATCC Deposit No:Z identified for example, in Table 1A and/or 1B. In one embodiment, antisense sequence is generated internally,  
10    by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991);  
15    Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

          For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the  
20    growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for *in vivo* use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is  
25    flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

          For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of  
30    the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into receptor polypeptide.

35            In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector

would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least

50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other

(Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells which express *in vivo*. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.



The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

5           The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

          The antagonist/agonist may also be employed to treat the diseases described herein.

          Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with  
10   overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

#### **Binding Peptides and Other Molecules**

15           The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

20           This method comprises the steps of:  
                                  contacting polypeptides of the invention with a plurality of molecules;  
                                  and  
                                  identifying a molecule that binds the polypeptides of the invention.

          The step of contacting the polypeptides of the invention with the plurality of molecules  
25   may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptides of the invention. The molecules having a selective affinity for the polypeptides can  
30   then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

          Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate  
35   the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its

outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptides of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptides and the individual clone. Prior to contacting the polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for polypeptides of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptides of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of the polypeptides of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptides of the invention or the plurality of polypeptides are bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind polypeptides of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature* 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, *Science* 249:386-390; Devlin et al., 1990, *Science*, 249:404-406; Christian, R. B., et al., 1992, *J. Mol. Biol.* 227:711-718; Lenstra, 1992, *J. Immunol. Meth.* 152:149-157; Kay et al., 1993, *Gene* 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds polypeptides of the invention can be carried out by contacting the library members with polypeptides of the

invention immobilized on a solid phase and harvesting those library members that bind to the polypeptides of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited  
5 herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to polypeptides of the invention.

10 Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

15 Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present  
20 invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to  
25 about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

### 30 **Other Activities**

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide,  
35 polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

5 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth,  
10 therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

15 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

20 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

25 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be  
30 used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

35 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

#### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in column 5, "ORF (From-To)", in Table 1B.1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in columns 8 and 9, "NT From" and "NT To" respectively, in Table 2.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in column 5, "ORF (From-To)", in Table 1B.1.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in columns 8 and 9, "NT From" and "NT To", respectively, in Table 2.

5 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z.

10 Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in ATCC Deposit No:Z, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide  
15 sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises the cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides of the cDNA  
20 sequence contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence  
25 which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z.

30 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a  
35 sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the

complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of the cDNA contained in ATCC Deposit No:Z.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; or the cDNA contained in ATCC Deposit No:Z which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence of cDNA contained in ATCC Deposit No:Z.



The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; the nucleotide sequence as defined in column 5 of Table 1B.1 or columns 8 and 9 of Table 2 or the complementary strand thereto; and a nucleotide sequence encoded by cDNA contained in ATCC Deposit No:Z. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000, or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A and/or 1B; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA "Clone ID" in Table 1A and/or 1B.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by

SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least  
5 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by contained in ATCC Deposit No:Z

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by cDNA contained in ATCC Deposit No:Z; a polypeptide encoded by SEQ ID NO:X or the complementary strand  
10 thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and/or the polypeptide sequence of SEQ ID NO:Y.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least  
15 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA contained in  
20 ATCC Deposit No:Z.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand  
25 thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide  
30 sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the  
35 sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1A, 1B or Table 2 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is a polypeptide molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2; and a polypeptide encoded by the cDNA contained in ATCC Deposit No:Z. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or

analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a specific delivery of toxic compositions to diseased cells (e.g., tumors, leukemias or lymphomas), which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide of the invention, including, but not limited to a binding agent, or antibody of the claimed invention that are associated with toxin or cytotoxic prodrugs.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

#### **Description of Table 6**

Table 6 summarizes some of the ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application. These deposits were made in addition to those described in the Table 1A.

**Table 6**

<b>ATCC Deposits</b>	<b>Deposit Date</b>	<b>ATCC Designation Number</b>
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

## Examples

### *Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

Each ATCC Deposit No:Z is contained in a plasmid vector. Table 7 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 7 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSPORT 2.0	pCMVSPORT 2.0
pCMVSPORT 3.0	pCMVSPORT 3.0
pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS-. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993)). Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be

transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991)). Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 7, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 1A, Table 2, Table 6 and Table 7 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each ATCC Deposit No:Z.

**TABLE 7**

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKE HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lambda ZAP II	LP01
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEI	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, frac A;re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPE	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPD HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUVC HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD	Human Activated T-Cells	Uni-ZAP XR	LP03



Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTAE			
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTf	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
HCDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE HTLf	Human adult testis, large inserts	Uni-ZAP XR	LP03
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HNFA HNFB HNFC HNFD HNFE HNFF HNFG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re- excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re-excision	pBS	LP03
HBMB HBMC HBMD	Human Bone Marrow, re- excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	HL-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
HTXJ HTXK	Activated T- cell(12h)/Thiouridine-re- excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSD HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL - OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE HSQF HSQG	Stromal cell TF274	Uni-ZAP XR	LP03
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLF HSLG	Smooth muscle, control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex, epileptic; re- excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced, re-exc	pBS	LP03
HFCA HFCE HFCC HFCD HFCE HFCE	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPC	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNB HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalmus,Schizophrenia	Uni-ZAP XR	LP04
HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD HNHE HNHF HNHG HNHH HNHI HNHI	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
HSDB HSDC	STRIATUM DEPRESSION	Uni-ZAP XR	LP04
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNFa and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAB HMAD HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimer's, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HMIA HMIB HMIC	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF-a	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSPORT 1	LP06
HOFM HOFN HOFO	H. Ovarian Tumor, II, OV5232	pCMVSPORT 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSPORT 2.0	LP07
HCGL	CD34+cells, II	pCMVSPORT 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSPORT 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSPORT 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSPORT2.0	LP07
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSPORT 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSPORT2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSPORT2.0	LP07
HNDA	Nasal polyps	pCMVSPORT2.0	LP07
HDRA	H. Primary Dendritic Cells,lib 3	pCMVSPORT2.0	LP07
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSPORT2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSPORT3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSPORT3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSPORT3.0	LP08
HNTA	NTERA2, control	pCMVSPORT3.0	LP08
HDP A HDPB HDPC HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSPORT3.0	LP08
HDP M HDPN HDPO HDPP	Primary Dendritic cells,frac 2	pCMVSPORT3.0	LP08
HMUA HMUB HMUC	Myeloid Progenitor Cell Line	pCMVSPORT3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSPORT3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSPORT3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSPORT3.0	LP08
HJMA HJMB	Human endometrial stromal cells-treated with progesterone	pCMVSPORT3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells-treated with estradiol	pCMVSPORT3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSPORT3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSPORT3.0	LP08

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSPORT3.0	LP08
HMTM	PCR, pBMC I/C treated	PCR II	LP09
HMJA	H. Meningioma, M6	pSport 1	LP10
HMKA HMKB HMKC HMKD HMKE	H. Meningioma, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD HADE HADF HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library, II	pSport 1	LP10
HMMA	Spleen metastatic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell, I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells, CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac 2	pSport 1	LP10
HLDX	Human Liver, normal, CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells, untreated	pSport 1	LP10
HUMA	Human Dermal Endothelial cells, treated	pSport 1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport 1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport 1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport 1	LP10
HFNA	Human ovary tumor cell	pSport 1	LP10

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	OV350721		
HKGA HKGB HKGC HKGD	Merkel Cells	pSport1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate,BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH,Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFIH HFII HFIJ	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Mesangial cell, frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
HFIX HFY HFIZ	Synovial Fibroblasts (IL1/TNF), subt	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSport 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSport 1	LP012
HBBA HBBC	Human Brain	pCMVSport 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSport 1	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSport 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSport 2.0	LP012
HAMF HAMG	KMH2	pCMVSport 3.0	LP012
HAJA HAJB HAJC	L428	pCMVSport 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSport 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSport 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSport 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSport 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound; 7.5 hours post incision	pCMVSport 3.0	LP012
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSport 3.0	LP012
HBIM	Olfactory epithelium; nasalcavity	pCMVSport 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSport 3.0	LP012
HWEA	Healing Abdomen Wound;15 days post incision	pCMVSport 3.0	LP012
HWJA	Healing Abdomen Wound;21&29 days	pCMVSport 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meningioma, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningioma, M1	pSport1	LP012
HOFA	Ovarian Tumor I, OV5232	pSport1	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport1	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
HMMA HMMB HMMC	Spleen metastatic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Fetal Thymus	pSport1	LP012
HDUA	Pericardium	pSport1	LP012
HBZA	Prostate,BPH, Lib 2	pSport1	LP012
HWCA	Larynx tumor	pSport1	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma,treated	pSport1	LP012
HBHM	Normal trachea	pSport1	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSport1	LP012
HMZA	Pharynx carcinoma	pSport1	LP012
HABG	Cheek Carcinoma	pSport1	LP012
HMZM	Pharynx Carcinoma	pSport1	LP012
HDRM	Larynx Carcinoma	pSport1	LP012
HVAA	Pancreas normal PCA4 No	pSport1	LP012
HICA	Tongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKE	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HL1S	LNCAp, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression,	pBluescript	LP013



Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	subtracted		
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFCA HFCE HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUVC HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPP HAPQ HAPR	Human Adult Pulmonary;re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma;re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart;re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCB HMCH HMCI HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013
HKFB	K562 + PMA (36 hrs),re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood),re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC.HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013
HAVM	Temporal cortex-Alzheimer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HAJR	Larynx normal	pSport 1	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
HWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport 1	LP014
HBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014
HBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
HWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
HWLA HWLB HWLC	Normal colon	pSport 1	LP014
HWLM HWLN	Colon Tumor	pSport 1	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
HAQM HAQN	Salivary Gland	pSport 1	LP014
HASM	Stomach; normal	pSport 1	LP014
HBCM	Uterus; normal	pSport 1	LP014
HCDM	Testis; normal	pSport 1	LP014
HDJM	Brain; normal	pSport 1	LP014
HEFM	Adrenal Gland,normal	pSport 1	LP014
HBAA	Rectum normal	pSport 1	LP014
HFDM	Rectum tumour	pSport 1	LP014
HGAM	Colon, normal	pSport 1	LP014
HHMM	Colon, tumour	pSport 1	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015
HHAM	Hypothalamus, Alzheimer's	pCMVSport 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2, Dexamethosome Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HRMA	Lung Mesothelium	pSport 1	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu treated	pTrip1Ex2	LP021
HFHM,HFHN	Ficolled Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	pSPORT1	LP022
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA,HUJB,HUJC,HUJD,HUJE	B-Cells	pCMVSPORT 3.0	LP022

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HNOA,HNOB,HNOC,HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLM	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA,HUUB,HUUC,HUUD	B-cells (unstimulated)	pTrip1Ex2	LP022
HWWA,HWWB,HWWC,HWW D,HWWE,HWWF,HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSPORT 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCP HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBT HNBH HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCJ	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCK HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

Two nonlimiting examples are provided below for isolating a particular clone from the deposited sample of plasmid cDNAs cited for that clone in Table 7. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982)). The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited

above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $MgCl_2$ , 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993)).

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for

PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

5                    ***Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide***

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X according to the method described in Example 1. (See also, Sambrook.)

10

***Example 3: Tissue specific expression analysis***

15                    The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue and/or disease specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs and assembled contigs which show tissue specific expression are selected.

20                    The original clone from which the specific EST sequence was generated, or in the case of an assembled contig, the clone from which the 5' most EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured and then transferred in 96 or 384 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. 25                    These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

30                    Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed (e.g., prostate, prostate cancer, ovarian, ovarian cancer, etc.). The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

35                    Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified.

#### ***Example 4: Chromosomal Mapping of the Polynucleotides***

An oligonucleotide primer set is designed according to the sequence at the 5' end of  
5 SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used  
in a polymerase chain reaction under the following set of conditions: 30 seconds, 95°C; 1 minute,  
56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C.  
Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel  
containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions are  
10 analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is  
determined by the presence of an approximately 100 bp PCR fragment in the particular somatic  
cell hybrid.

#### ***Example 5: Bacterial Expression of a Polypeptide***

15 A polynucleotide encoding a polypeptide of the present invention is amplified using  
PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined  
in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert  
should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in  
20 order to clone the amplified product into the expression vector. For example, BamHI and XbaI  
correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc.,  
Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of  
replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a  
6-histidine tag (6-His), and restriction enzyme cloning sites.

25 The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is  
ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The  
ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains  
multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers  
kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates  
30 and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed  
by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in  
LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used  
to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density  
35 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added



to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

DNA can be inserted into the pHE4a by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

***Example 6: Purification of a Polypeptide from an Inclusion Body***

5

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

10 Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

15 The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

20 The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

25 Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

30 To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

35 Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of

strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A<sub>280</sub> monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### ***Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System***

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al.,

"A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

5 The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

10 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment  
15 is confirmed by DNA sequencing.

Five µg of a plasmid containing the polynucleotide is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA, Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGold™ virus DNA and 5 µg of the  
20 plasmid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5  
25 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc.,  
30 Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant  
35 viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm

dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

#### *Example 8: Expression of a Polypeptide in Mammalian Cells*

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable

marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

### ***Example 9: Protein Fusions***

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988)). Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time *in vivo*. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (ATCC Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

5

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCC  
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGGA  
CACCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGCCAC  
10 GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCC  
AAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTC  
ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC  
AAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA  
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTC  
15 AGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAG  
AGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC  
GGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG  
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGA  
GCCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID  
20 NO: 1)

#### ***Example 10: Production of an Antibody from a Polypeptide***

##### **a) Hybridoma Technology**

25 The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of a polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a  
30 preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for a polypeptide of the present invention are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal  
35 Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with a polypeptide of the present invention or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any



suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line.

5 Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones  
10 which secrete antibodies capable of binding the polypeptide of the present invention .

Alternatively, additional antibodies capable of binding to a polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific  
15 antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide-specific antibody can be blocked by said polypeptide. Such antibodies comprise anti-idiotypic antibodies to the polypeptide-specific antibody and are used to immunize an animal to induce formation of further  
20 polypeptide-specific antibodies.

For *in vivo* use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al.,  
25 BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., International Publication No. WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985)).

#### 30 b) Isolation Of Antibody Fragments Directed Against a Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against a polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated  
35 herein by reference in its entirety).

*Rescue of the Library.* A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody

fragments, approximately  $10^9$  *E. coli* harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU,  $2 \times 10^8$  TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in International Publication No. WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37°C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately  $10^{13}$  transducing units/ml (ampicillin-resistant clones).

*Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately  $10^{13}$  TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log *E. coli* TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The *E. coli* are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

*Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect *E. coli* HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 µg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are

further characterized by PCR fingerprinting (see, e.g., International Publication No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

***Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide***

RNA isolated from entire families or individual patients presenting with diabetes mellitus is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X; and/or the nucleotide sequence of the cDNA contained in ATCC Deposit No:Z. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase (Epicentre Technologies). The intron-exon boundaries of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations are then cloned and sequenced to validate the results of the direct sequencing.

PCR products are cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenin deoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991)). Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic

region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

***Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological***

***Sample***

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbound polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbound conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

***Example 13: Formulation***

The invention also provides methods of preventing, treating and/or ameliorating diabetes mellitus by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The  
5 "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans  
10 between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on  
15 the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of  
20 any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally,  
25 parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal,  
30 subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil)  
35 or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

In a preferred embodiment, polypeptide, polynucleotide, and antibody compositions of the invention are formulated in a biodegradable, polymeric drug delivery system, for example as described in U.S. Patent Nos. 4,938,763; 5,278,201; 5,278,202; 5,324,519; 5,340,849; and 5,487,897 and in International Publication Numbers WO01/35929, WO00/24374, and WO00/06117 which are hereby incorporated by reference in their entirety. In specific preferred embodiments the polypeptide, polynucleotide, and antibody compositions of the invention are formulated using the ATRIGEL® Biodegradable System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

Examples of biodegradable polymers which can be used in the formulation of polypeptide, polynucleotide, and antibody compositions, include but are not limited to, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those that have a lower degree of crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more amorphous regions to enhance solubility. In specific preferred embodiments, the biodegradable polymers which can be used in the formulation of polypeptide, polynucleotide, and antibody compositions are poly(lactide-co-glycolides). Polymer properties such as molecular weight, hydrophobicity, and lactide/glycolide ratio may be modified to obtain the desired polypeptide, polynucleotide, or antibody release profile (See, e.g., Ravivarapu et al., Journal of Pharmaceutical Sciences 89:732-741 (2000), which is hereby incorporated by reference in its entirety).

It is also preferred that the solvent for the biodegradable polymer be non-toxic, water miscible, and otherwise biocompatible. Examples of such solvents include, but are not limited to, N-methyl-2-pyrrolidone, 2-pyrrolidone, C2 to C6 alkanols, C1 to C15 alcohols, dils, triols, and tetraols such as ethanol, glycerine propylene glycol, butanol; C3 to C15 alkyl ketones such as

acetone, diethyl ketone and methyl ethyl ketone; C3 to C15 esters such as methyl acetate, ethyl acetate, ethyl lactate; alkyl ketones such as methyl ethyl ketone, C1 to C15 amides such as dimethylformamide, dimethylacetamide and caprolactam; C3 to C20 ethers such as tetrahydrofuran, or solketal; tweens, triacetin, propylene carbonate, decylmethylsulfoxide, dimethyl sulfoxide, oleic acid, 1-dodecylazacycloheptan-2-one, Other preferred solvents are benzyl alcohol, benzyl benzoate, dipropylene glycol, tributyrin, ethyl oleate, glycerin, glycofural, isopropyl myristate, isopropyl palmitate, oleic acid, polyethylene glycol, propylene carbonate, and triethyl citrate. The most preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, triacetin, and propylene carbonate because of the solvating ability and their compatibility.

Additionally, formulations comprising polypeptide, polynucleotide, and antibody compositions and a biodegradable polymer may also include release-rate modification agents and/or pore-forming agents. Examples of release-rate modification agents include, but are not limited to, fatty acids, triglycerides, other like hydrophobic compounds, organic solvents, plasticizing compounds and hydrophilic compounds. Suitable release rate modification agents include, for example, esters of mono-, di-, and tricarboxylic acids, such as 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, diethyl phthalate, dimethyl phthalate, dibutyl phthalate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, glycerol triacetate, di(n-butyl) sebecate, and the like; polyhydroxy alcohols, such as propylene glycol, polyethylene glycol, glycerin, sorbitol, and the like; fatty acids; triesters of glycerol, such as triglycerides, epoxidized soybean oil, and other epoxidized vegetable oils; sterols, such as cholesterol; alcohols, such as C.sub.6 -C.sub.12 alkanols, 2-ethoxyethanol. The release rate modification agent may be used singly or in combination with other such agents. Suitable combinations of release rate modification agents include, but are not limited to, glycerin/propylene glycol, sorbitol/glycerine, ethylene oxide/propylene oxide, butylene glycol/adipic acid, and the like. Preferred release rate modification agents include, but are not limited to, dimethyl citrate, triethyl citrate, ethyl heptanoate, glycerin, and hexanediol. Suitable pore-forming agents that may be used in the polymer composition include, but are not limited to, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. Solid crystals that will provide a defined pore size, such as salt or sugar, are preferred.

In specific preferred embodiments the polypeptide, polynucleotide, and antibody compositions of the invention are formulated using the BEMA™ BioErodible Mucoadhesive System, MCA™ MucoCutaneous Absorption System, SMP™ Solvent MicroParticle System, or BCPT™ BioCompatible Polymer System of Atrix Laboratories, Inc. (Fort Collins, Colorado).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see generally*, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci.(USA)* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or



sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis.

Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate  
5 intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics,  
10 steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g.,  
15 as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium  
20 (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROMET™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are administered in combination with heparin and  
25 aspirin.

In another embodiment, the Therapeutics of the invention are administered in combination with thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue  
35 plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, compositions of the invention are administered in combination with tissue

plasminogen activator and aspirin.

In another embodiment, the Therapeutics of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g.,  
5 PERSANTINE™), and ticlopidine (e.g., TICLID™).

In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the detection, prevention, diagnosis, prognostication, treatment, and/or amelioration of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis,  
10 myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for  
15 reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™  
25 (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™  
30 (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

35 Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but

with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is  
5 PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'-azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of  $\beta$ -L-FD4C and  $\beta$ -L-FddC (WO 98/17281).

10 Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N  
15 mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott  
20 Laboratories); BMS-232632 (an azapeptide; Bristol-Myers Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-  
25 175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Wellcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents  
30 transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18  
35 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists

such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine receptor agonists such as RANTES, SDF-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors  
5 include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compounds such as BCX-34 (a  
10 purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral  
15 genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines  
20 such as MIP-1 $\alpha$ , MIP-1 $\beta$ , SDF-1 $\alpha$ , IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN- $\alpha$ 2a; antagonists of TNFs, NF $\kappa$ B, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and  
25 fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targeted to the ER to block surface  
30 expression of newly synthesized CCR5 (Yang *et al.*, *PNAS* 94:11567-72 (1997); Chen *et al.*, *Nat. Med.* 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF- $\alpha$  antibodies, and monoclonal antibody 33A; aryl  
35 hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-

pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and  $\alpha$ -naphthoflavone (WO 98/30213); and antioxidants such as  $\gamma$ -L-glutamyl-L-cysteine ethyl ester ( $\gamma$ -GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the  
5 Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to,  
10 TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™,  
15 LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in  
20 any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In  
25 another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In  
30 another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another  
35 specific embodiment, Therapeutics of the invention are used in any combination with

LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the  
5 Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

10 In other embodiments, the Therapeutics of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the Therapeutics of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

15 In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by  
20 suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine),  
25 PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to  
30 prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™,  
35 ATGAM™ (antithymocyte globulin), and GAMIMUNE™. In a specific embodiment,

Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. 5 betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, 10 phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, 15 emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, 20 Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, 25 tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and 30 orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo 35 complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten



(VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlitin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting

proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositions of the invention include, but are not limited to, EMD-121974 (Merck KGaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcosine), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazines (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone propionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing hormone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal

anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are <sup>90</sup>Y and <sup>111</sup>In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No.

WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol,

bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to,  $^{127}\text{I}$ , radioactive isotopes of iodine such as  $^{131}\text{I}$  and  $^{123}\text{I}$ ; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T<sub>4</sub>™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T<sub>3</sub>™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol;  $\text{Ca}^{2+}$  channel blockers;

dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or conjugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), 5 PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), 10 MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ 15 (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, 20 NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; 25 parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ 30 (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotrophic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), 35 BECLOVENT™ and VANCERIL™ (beclo-metasone dipropionate), CELESTONE™

(betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™

5 (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™

10 (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide),

15 FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™

20 (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide);

25 inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone); bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide),

30 TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), ciglitazone, pioglitazone, and alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide).



In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B<sub>12</sub>, cyanocobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril,trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nifedipine, nimodipine, and verapamil.

In certain embodiments, the Therapeutics of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the Therapeutic of the invention include, but are not limited to, H<sub>2</sub> histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of H<sup>+</sup>, K<sup>+</sup> ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

5

***Example 14: Method of Treating Decreased Levels of the Polypeptide***

10 The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of polypeptides (including agonists thereto), and/or antibodies of the invention. Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual may be treated by administering agonists of said polypeptide.

15 Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist (including polypeptides and antibodies of the present invention) to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-  
20 100 ug/kg of the agonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

***Example 15: Method of Treating Increased Levels of the Polypeptide***

25 The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of  
30 the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The  
35 antisense polynucleotides of the present invention can be formulated using techniques and formulations described herein (e.g. see Example 13), or otherwise known in the art.

### *Example 16: Method of Treatment Using Gene Therapy-Ex Vivo*

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed

and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

5           The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

***Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention***

10           Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; 15 International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

20           Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' 25 ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

30           The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel, then purified by phenol extraction and ethanol precipitation.

35           In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

5 Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM  
10 HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub> HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3X10<sup>6</sup> cells/ml. Electroporation should be performed immediately following resuspension.

15 Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a  
20 HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

25 Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately 1.5X10<sup>6</sup> cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V, respectively. As voltage increases, cell  
30 survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are  
35 added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

5                    ***Example 18: Method of Treatment Using Gene Therapy - In Vivo***

Another aspect of the present invention is using *in vivo* gene therapy methods to prevent, treat, and/or ameliorate diabetes mellitus. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an  
10 animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res.  
15 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart,  
20 muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like.  
25 However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably  
30 constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced  
35 into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph,

blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by

excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

#### *Example 19: Transgenic Animals*

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies



such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

### Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (e.g., see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and “knock-out” animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### ***Example 21: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models***

##### *Diabetic db+/db+ Mouse Model.*

To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31

(*Suppl*):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

### *Steroid Impaired Rat Model*

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating

monocytes (Haynes et al., *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In: Antiinflammatory Steroid Action: Basic and Clinical Aspects*, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck et al., *Growth Factors.* 5: 295-304 (1991); Haynes et al., *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In: Antiinflammatory Steroid Action: Basic and Clinical Aspects*, Academic Press, New York, pp. 280-302 (1989); Pierce et al., *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are

placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

#### ***Example 22: Production Of Polypeptide of the Invention For High-Throughput Screening Assays***

The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 24-27.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

5 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the  
10 Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks.  
15 By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates.  
20 Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L  
25 of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose;  
30 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-  
35 Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; and 99.65 mg/ml of L-



Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES  
5 Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with  
10 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml  
15 appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 24-27.

20 It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by  
25 an activity in a particular assay.

### ***Example 23: Construction of GAS Reporter Construct***

One signal transduction pathway involved in the differentiation and proliferation of  
30 cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal  
35 Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is

widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

5           The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase (“Jaks”) family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

10           The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995)). A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-15 10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xaa-Trp-Ser (SEQ ID NO: 2)).

20           Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway (See Table below). Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

25

<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u>				<u>STATS</u> <u>GAS(elements) or ISRE</u>
		<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
<u>IFN family</u>						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
<u>gp130 family</u>						
IL-6 (Pleiotropic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotropic)	?	+	?	?	1,3	
OnM(Pleiotropic)	?	+	+	?	1,3	
LIF(Pleiotropic)	?	+	+	?	1,3	
CNTF(Pleiotropic)	-/+	+	+	?	1,3	
G-CSF(Pleiotropic)	?	+	?	?	1,3	
IL-12(Pleiotropic)	+	-	+	+	1,3	
<u>g-C family</u>						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
<u>gp140 family</u>						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
<u>Growth hormone family</u>						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-
CAS>IRF1=IFP>>Ly6)						
<u>Receptor Tyrosine Kinases</u>						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO: 3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO: 4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTCC  
CCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC  
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTT  
TTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTCCAGAAGTAGTGA  
GGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO: 5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo

vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence, for example, with EGR and NF-KB promoter sequences. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

#### ***Example 24: Assay for SEAP Activity***

SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the Table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25

20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

***Example 25: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability***

5

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

10

The following assay uses Fluorometric Imaging Plate Reader (“FLIPR”) to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any

fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells  
5 are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with  
10 HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to  
15 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

20 To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present  
25 invention, which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

#### ***Example 26: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity***

30 The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but  
35 also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine  
5 kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction  
10 pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and  
15 dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of  
20 alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne  
25 plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 22, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from  
30 Boehringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well,



after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

5 Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from  
10 Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of  
15 Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

20 Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for  
25 one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

#### 30 ***Example 27: High-Throughput Screening Assay Identifying Phosphorylation Activity***

As a potential alternative and/or complement to the assay of protein tyrosine kinase  
35 activity described in Example 26, an assay which detects activation (phosphorylation) of major

intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyn filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 22 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

#### ***Example 28: Detection of Inhibition of a Mixed Lymphocyte Reaction***

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and

natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10  $\mu$ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1  $\mu$ C of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

#### ***Example 29: Assays for Protease Activity***

The following assay may be used to assess protease activity of the polypeptides of the invention.

Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)).

Samples are run on 10% polyacrylamide/0.1% SDS gels containing 1% gelatin or casein, soaked in

2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis appear as clear areas against the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mMNaPO<sub>4</sub>, 1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive control.

Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983)).

#### Example 30: Identifying Serine Protease Substrate Specificity

Methods known in the art or described herein may be used to determine the substrate specificity of the polypeptides of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

#### Example 31: Ligand Binding Assays

The following assay may be used to assess ligand binding activity of the polypeptides of the invention.

Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for a polypeptide is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards its polypeptide. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

***Example 32: Functional Assay in *Xenopus* Oocytes***

Capped RNA transcripts from linearized plasmid templates encoding the polypeptides of the invention are synthesized in vitro with RNA polymerases in accordance with standard  
5 procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/ml. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocyte) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response polypeptides and polypeptide agonist exposure. Recordings are made in Ca<sup>2+</sup> free  
10 Barth's medium at room temperature. The *Xenopus* system can be used to screen known ligands and tissue/cell extracts for activating ligands.

***Example 33: Microphysiometric Assays***

15 Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the  
20 activation of polypeptide which is coupled to an energy utilizing intracellular signaling pathway.

***Example 34: Extract/Cell Supernatant Screening***

25 A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the polypeptides of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify its natural ligands. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is  
30 isolated and identified.

***Example 35: Calcium and cAMP Functional Assays***

Seven transmembrane receptors which are expressed in HEK 293 cells have been shown to be coupled functionally to activation of PLC and calcium mobilization and/or cAMP stimulation or inhibition. Basal calcium levels in the HEK 293 cells in receptor-transfected or vector control cells were observed to be in the normal, 100 nM to 200 nM, range. HEK 293 cells expressing recombinant receptors are loaded with fura 2 and in a single day >150 selected ligands or tissue/cell extracts are evaluated for agonist induced calcium mobilization. Similarly, HEK 293 cells expressing recombinant receptors are evaluated for the stimulation or inhibition of cAMP production using standard cAMP quantitation assays. Agonists presenting a calcium transient or cAMP fluctuation are tested in vector control cells to determine if the response is unique to the transfected cells expressing receptor.

#### ***Example 36: ATP-binding assay***

The following assay may be used to assess ATP-binding activity of polypeptides of the invention.

ATP-binding activity of the polypeptides of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,858,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to polypeptides of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of the ABC transport protein of the present invention are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenylyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP (<sup>32</sup>P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the particular polypeptides of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenylyl-5'-imidodiphosphate provides a measure of ATP affinity to the polypeptides.

#### ***Example 37: Small Molecule Screening***

This invention is particularly useful for screening therapeutic compounds by using the

polypeptides of the invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and polypeptide of the invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the invention. These methods comprise contacting such an agent with a polypeptide of the invention or fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is herein incorporated by reference in its entirety. Briefly stated, large numbers of different small molecule test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with polypeptides of the invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

#### ***Example 38: Phosphorylation Assay***

In order to assay for phosphorylation activity of the polypeptides of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a

protein substrate using gamma-labeled  $^{32}\text{P}$ -ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The polypeptides of the invention are incubated with the protein substrate,  $^{32}\text{P}$ -ATP, and a kinase buffer. The  $^{32}\text{P}$  incorporated into the substrate is then separated from free  $^{32}\text{P}$ -ATP by electrophoresis, and the incorporated  $^{32}\text{P}$  is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the polypeptides of the invention.

***Example 39: Detection of Phosphorylation Activity (Activation) of the Polypeptides of the Invention in the Presence of Polypeptide Ligands***

Methods known in the art or described herein may be used to determine the phosphorylation activity of the polypeptides of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

***Example 40: Identification Of Signal Transduction Proteins That Interact With Polypeptides Of The Present Invention***

The purified polypeptides of the invention are research tools for the identification, characterization and purification of additional signal transduction pathway proteins or receptor proteins. Briefly, labeled polypeptides of the invention are useful as reagents for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptides of the invention are covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The protein complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

***Example 41: Assay for Phosphatase Activity***

The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of the polypeptides of the invention.



In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity is measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [<sup>32</sup>P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from <sup>32</sup>P-labeled MyBP.

***Example 42: Interaction of Serine/Threonine Phosphatases with other Proteins***

The polypeptides of the invention with serine/threonine phosphatase activity as determined in Example 41 are research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, labeled polypeptide(s) of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, polypeptide of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the polypeptides of the invention. The polypeptides of the invention -complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

***Example 43: Assaying for Heparanase Activity***

In order to assay for heparanase activity of the polypeptides of the invention, the heparanase assay described by Vlodavsky et al is utilized (Vlodavsky, I., et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media or intact cells ( $1 \times 10^6$  cells per 35-mm dish) are incubated for 18 hrs at 37°C, pH 6.2-6.6, with <sup>35</sup>S-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at  $0.5 < K_{av} < 0.8$  (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of the polypeptides of the invention in cleaving heparan sulfate.

#### ***Example 44: Immobilization of biomolecules***

5 This example provides a method for the stabilization of polypeptides of the invention in  
non-host cell lipid bilayer constructs (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999),  
hereby incorporated by reference in its entirety herein) which can be adapted for the study of  
polypeptides of the invention in the various functional assays described above. Briefly,  
carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to the extracellular  
domain of the polypeptides of the invention, thus allowing uniform orientation upon  
10 immobilization. A 50uM solution of polypeptides of the invention in washed membranes is  
incubated with 20 mM NaIO<sub>4</sub> and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-  
hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed  
(Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h,  
exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl,  
15 1 mM MgCl<sub>2</sub>, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is  
diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

#### ***Example 45: TAQMAN***

20

Quantitative PCR (QPCR). Total RNA from cells in culture are extracted by Trizol  
separation as recommended by the supplier (LifeTechnologies). (Total RNA is treated with DNase  
I (Life Technologies) to remove any contaminating genomic DNA before reverse transcription.)  
Total RNA (50 ng) is used in a one-step, 50ul, RT-QPCR, consisting of Taqman Buffer A (Perkin-  
25 Elmer; 50 mM KCl/10 mM Tris, pH 8.3), 5.5 mM MgCl<sub>2</sub>, 240 μM each dNTP, 0.4 units RNase  
inhibitor(Promega), 8%glycerol, 0.012% Tween-20, 0.05% gelatin, 0.3uM primers, 0.1uM probe,  
0.025units Amplitaq Gold (Perkin-Elmer) and 2.5 units Superscript II reverse transcriptase (Life  
Technologies). As a control for genomic contamination, parallel reactions are setup without  
reverse transcriptase. The relative abundance of (unknown) and 18S RNAs are assessed by using  
30 the Applied Biosystems Prism 7700 Sequence Detection System (Livak, K. J., Flood, S. J.,  
Marmaro, J., Giusti, W. & Deetz, K. (1995) PCR Methods Appl. 4, 357-362). Reactions are  
carried out at 48°C for 30 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15s, 60°C for 1  
min. Reactions are performed in triplicate.

Primers (f & r) and FRET probes sets are designed using Primer Express Software (Perkin-Elmer). Probes are labeled at the 5'-end with the reporter dye 6-FAM and on the 3'-end with the quencher dye TAMRA (Biosource International, Camarillo, CA or Perkin-Elmer).

#### *Example 46: Assays for Metalloproteinase Activity*

Metalloproteinases (EC 3.4.24.-) are peptide hydrolases which use metal ions, such as  $Zn^{2+}$ , as the catalytic mechanism. Metalloproteinase activity of polypeptides of the present invention can be assayed according to the following methods.

##### *Proteolysis of alpha-2-macroglobulin*

To confirm protease activity, purified polypeptides of the invention are mixed with the substrate alpha-2-macroglobulin (0.2 unit/ml; Boehringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM  $CaCl_2$ , 25  $\mu M$   $ZnCl_2$  and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyacrylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular weight bands as compared to the negative control.

##### *Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases*

Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND  $HgCl_2$ ), peptide metalloproteinase inhibitors (TIMP-1 and TIMP-2), and commercial small molecule MMP inhibitors) are used to characterize the proteolytic activity of polypeptides of the invention. The three synthetic MMP inhibitors used are: MMP inhibitor I, [ $IC_{50}$  = 1.0  $\mu M$  against MMP-1 and MMP-8;  $IC_{50}$  = 30  $\mu M$  against MMP-9;  $IC_{50}$  = 150  $\mu M$  against MMP-3]; MMP-3 (stromelysin-1) inhibitor I [ $IC_{50}$  = 5  $\mu M$  against MMP-3], and MMP-3 inhibitor II [ $K_i$  = 130 nM against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with purified polypeptides of the invention (50 $\mu g/ml$ ) in 22.9  $\mu l$  of 1x HEPES buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM  $CaCl_2$ , 25  $\mu M$   $ZnCl_2$  and 0.05%Brij-35) and incubated at room temperature (24 °C) for 2-hr, then 7.1  $\mu l$  of substrate alpha-2-macroglobulin (0.2 unit/ml) is added and incubated at 37°C for 20-hr. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

#### *Synthetic Fluorogenic Peptide Substrates Cleavage Assay*

The substrate specificity for polypeptides of the invention with demonstrated metalloproteinase activity can be determined using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) converting enzyme (TACE). All the substrates are prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500  $\mu$ M. Fluorescent assays are performed by using a Perkin Elmer LS 50B luminescence spectrometer equipped with a constant temperature water bath. The excitation  $\lambda$  is 328 nm and the emission  $\lambda$  is 393 nm. Briefly, the assay is carried out by incubating 176  $\mu$ l 1x HEPES buffer (0.2 M NaCl, 10 mM CaCl<sub>2</sub>, 0.05% Brij-35 and 50 mM HEPES, pH 7.5) with 4  $\mu$ l of substrate solution (50  $\mu$ M) at 25 °C for 15 minutes, and then adding 20  $\mu$ l of a purified polypeptide of the invention into the assay cuvet. The final concentration of substrate is 1  $\mu$ M. Initial hydrolysis rates are monitored for 30-min.

#### *Example 47: Characterization of the cDNA contained in a deposited plasmid*

The size of the cDNA insert contained in a deposited plasmid may be routinely determined using techniques known in the art, such as PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the cDNA sequence. For example, two primers of 17-30 nucleotides derived from each end of the cDNA (i.e., hybridizable to the absolute 5' nucleotide or the 3' nucleotide end of the sequence of SEQ ID NO:X, respectively) are synthesized and used to amplify the cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product. It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

### ***Incorporation by Reference***

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. In addition, the sequence listing submitted herewith is incorporated herein by reference in its entirety. The specification and sequence listing of each of the following U.S. and PCT applications are herein incorporated by reference in their entirety: U.S. Appln. No. 60/040,162 filed on 07-Mar-1997, U.S. Appln. No. 60/043,576 filed on 11-Apr-1997, U.S. Appln. No. 60/047,601 filed on 23-May-1997, U.S. Appln. No. 60/056,845 filed on 22-Aug-1997, U.S. Appln. No. 60/043,580 filed on 11-Apr-1997, U.S. Appln. No. 60/047,599 filed on 23-May-1997, U.S. Appln. No. 60/056,664 filed on 22-Aug-1997, U.S. Appln. No. 60/043,314 filed on 11-Apr-1997, U.S. Appln. No. 60/047,632 filed on 23-May-1997, U.S. Appln. No. 60/056,892 filed on 22-Aug-1997, U.S. Appln. No. 60/043,568 filed on 11-Apr-1997, U.S. Appln. No. 60/047,595 filed on 23-May-1997, U.S. Appln. No. 60/056,632 filed on 22-Aug-1997, U.S. Appln. No. 60/043,578 filed on 11-Apr-1997, U.S. Appln. No. 60/040,333 filed on 07-Mar-1997, U.S. Appln. No. 60/043,670 filed on 11-Apr-1997, U.S. Appln. No. 60/047,596 filed on 23-May-1997, U.S. Appln. No. 60/056,864 filed on 22-Aug-1997, U.S. Appln. No. 60/043,674 filed on 11-Apr-1997, U.S. Appln. No. 60/047,612 filed on 23-May-1997, U.S. Appln. No. 60/056,631 filed on 22-Aug-1997, U.S. Appln. No. 60/043,569 filed on 11-Apr-1997, U.S. Appln. No. 60/047,588 filed on 23-May-1997, U.S. Appln. No. 60/056,876 filed on 22-Aug-1997, U.S. Appln. No. 60/043,671 filed on 11-Apr-1997, U.S. Appln. No. 60/043,311 filed on 11-Apr-1997, U.S. Appln. No. 60/038,621 filed on 07-Mar-1997, U.S. Appln. No. 60/043,672 filed on 11-Apr-1997, U.S. Appln. No. 60/047,613 filed on 23-May-1997, U.S. Appln. No. 60/056,636 filed on 22-Aug-1997, U.S. Appln. No. 60/043,669 filed on 11-Apr-1997, U.S. Appln. No. 60/047,582 filed on 23-May-1997, U.S. Appln. No. 60/056,910 filed on 22-Aug-1997, U.S. Appln. No. 60/043,315 filed on 11-Apr-1997, U.S. Appln. No. 60/047,598 filed on 23-May-1997, U.S. Appln. No. 60/056,874 filed on 22-Aug-1997, U.S. Appln. No. 60/043,312 filed on 11-Apr-1997, U.S. Appln. No. 60/047,585 filed on 23-May-1997, U.S. Appln. No. 60/056,881 filed on 22-Aug-1997, U.S. Appln. No. 60/043,313 filed on 11-Apr-1997, U.S. Appln. No. 60/047,586 filed on 23-May-1997, U.S. Appln. No. 60/056,909 filed on 22-Aug-1997, U.S. Appln. No. 60/040,161 filed on 07-Mar-1997, U.S. Appln. No. 60/047,587 filed on 23-May-1997, U.S. Appln. No. 60/056,879 filed on 22-Aug-1997, U.S. Appln. No. 60/047,500 filed on 23-May-1997, U.S. Appln. No. 60/056,880 filed on 22-Aug-1997, U.S. Appln. No. 60/047,584 filed on 23-May-1997, U.S. Appln. No. 60/056,894 filed on 22-Aug-1997, U.S. Appln. No. 60/047,492 filed on 23-May-1997, U.S. Appln. No. 60/056,911 filed on 22-Aug-1997, U.S. Appln. No. 60/040,626 filed on 07-Mar-1997, U.S. Appln. No. 60/047,503 filed on 23-May-1997, U.S. Appln. No.

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18-Aug-1997, U.S. Appln. No. 60/051,916 filed on 08-Jul-1997, U.S. Appln. No. 60/055,953 filed on 18-Aug-1997, U.S. Appln. No. 60/051,930 filed on 08-Jul-1997, U.S. Appln. No. 60/055,950 filed on 18-Aug-1997, U.S. Appln. No. 60/051,918 filed on 08-Jul-1997, U.S. Appln. No. 60/055,947 filed on 18-Aug-1997, U.S. Appln. No. 60/051,920 filed on 08-Jul-1997, U.S. Appln. No. 60/055,964 filed on 18-Aug-1997, U.S. Appln. No. 60/052,733 filed on 08-Jul-1997, U.S. Appln. No. 60/056,360 filed on 18-Aug-1997, U.S. Appln. No. 60/052,795 filed on 08-Jul-1997, U.S. Appln. No. 60/055,684 filed on 18-Aug-1997, U.S. Appln. No. 60/051,919 filed on 08-Jul-1997, U.S. Appln. No. 60/055,984 filed on 18-Aug-1997, U.S. Appln. No. 60/051,928 filed on 08-Jul-1997, U.S. Appln. No. 60/055,954 filed on 18-Aug-1997, U.S. Appln. No. 60/052,870 filed on 16-Jul-1997, U.S. Appln. No. 60/055,952 filed on 18-Aug-1997, U.S. Appln. No. 60/052,871 filed on 16-Jul-1997, U.S. Appln. No. 60/055,725 filed on 18-Aug-1997, U.S. Appln. No. 60/052,872 filed on 16-Jul-1997, U.S. Appln. No. 60/056,359 filed on 18-Aug-1997, U.S. Appln. No. 60/052,661 filed on 16-Jul-1997, U.S. Appln. No. 60/055,985 filed on 18-Aug-1997, U.S. Appln. No. 60/052,874 filed on 16-Jul-1997, U.S. Appln. No. 60/055,724 filed on 18-Aug-1997, U.S. Appln. No. 60/052,873 filed on 16-Jul-1997, U.S. Appln. No. 60/055,726 filed on 18-Aug-1997, U.S. Appln. No. 60/052,875 filed on 16-Jul-1997, U.S. Appln. No. 60/056,361 filed on 18-Aug-1997, U.S. Appln. No. 60/053,440 filed on 22-Jul-1997, U.S. Appln. No. 60/055,989 filed on 18-Aug-1997, U.S. Appln. No. 60/053,441 filed on 22-Jul-1997, U.S. Appln. No. 60/055,946 filed on 18-Aug-1997, U.S. Appln. No. 60/053,442 filed on 22-Jul-1997, U.S. Appln. No. 60/055,683 filed on 18-Aug-1997, U.S. Appln. No. 60/054,212 filed on 30-Jul-1997, U.S. Appln. No. 60/055,968 filed on 18-Aug-1997, U.S. Appln. No. 60/054,209 filed on 30-Jul-1997, U.S. Appln. No. 60/055,972 filed on 18-Aug-1997, U.S. Appln. No. 60/054,234 filed on 30-Jul-1997, U.S. Appln. No. 60/055,969 filed on 18-Aug-1997, U.S. Appln. No. 60/055,386 filed on 05-Aug-1997, U.S. Appln. No. 60/055,986 filed on 18-Aug-1997, U.S. Appln. No. 60/054,807 filed on 05-Aug-1997, U.S. Appln. No. 60/055,970 filed on 18-Aug-1997, U.S. Appln. No. 60/054,215 filed on 30-Jul-1997, U.S. Appln. No. 60/056,543 filed on 19-Aug-1997, U.S. Appln. No. 60/054,218 filed on 30-Jul-1997, U.S. Appln. No. 60/056,561 filed on 19-Aug-1997, U.S. Appln. No. 60/054,214 filed on 30-Jul-1997, U.S. Appln. No. 60/056,534 filed on 19-Aug-1997, U.S. Appln. No. 60/054,236 filed on 30-Jul-1997, U.S. Appln. No. 60/056,729 filed on 19-Aug-1997, U.S. Appln. No. 60/054,213 filed on 30-Jul-1997, U.S. Appln. No. 60/056,727 filed on 19-Aug-1997, U.S. Appln. No. 60/054,211 filed on 30-Jul-1997, U.S. Appln. No. 60/056,554 filed on 19-Aug-1997, U.S. Appln. No. 60/054,217 filed on 30-Jul-1997, U.S. Appln. No. 60/056,730 filed on 19-Aug-1997, U.S. Appln. No. 60/055,312 filed on 05-Aug-1997, U.S. Appln. No. 60/056,563 filed on 19-Aug-1997, U.S. Appln. No. 60/055,309 filed on 05-Aug-1997, U.S. Appln. No. 60/056,557 filed on 19-Aug-1997, U.S. Appln. No. 60/055,310 filed on 05-Aug-1997, U.S. Appln. No. 60/056,371 filed on 19-

Aug-1997, U.S. Appln. No. 60/054,798 filed on 05-Aug-1997, U.S. Appln. No. 60/056,732 filed  
 on 19-Aug-1997, U.S. Appln. No. 60/056,369 filed on 19-Aug-1997, U.S. Appln. No. 60/056,535  
 filed on 19-Aug-1997, U.S. Appln. No. 60/056,556 filed on 19-Aug-1997, U.S. Appln. No.  
 60/056,555 filed on 19-Aug-1997, U.S. Appln. No. 60/054,806 filed on 05-Aug-1997, U.S. Appln.  
 5 No. 60/056,366 filed on 19-Aug-1997, U.S. Appln. No. 60/054,809 filed on 05-Aug-1997, U.S.  
 Appln. No. 60/056,364 filed on 19-Aug-1997, U.S. Appln. No. 60/054,804 filed on 05-Aug-1997,  
 U.S. Appln. No. 60/056,370 filed on 19-Aug-1997, U.S. Appln. No. 60/054,803 filed on 05-Aug-  
 1997, U.S. Appln. No. 60/056,731 filed on 19-Aug-1997, U.S. Appln. No. 60/055,311 filed on 05-  
 Aug-1997, U.S. Appln. No. 60/056,365 filed on 19-Aug-1997, U.S. Appln. No. 60/054,808 filed  
 10 on 05-Aug-1997, U.S. Appln. No. 60/056,367 filed on 19-Aug-1997, U.S. Appln. No. 60/056,726  
 filed on 19-Aug-1997, U.S. Appln. No. 60/056,368 filed on 19-Aug-1997, U.S. Appln. No.  
 60/056,728 filed on 19-Aug-1997, U.S. Appln. No. 60/056,628 filed on 19-Aug-1997, U.S. Appln.  
 No. 60/056,629 filed on 19-Aug-1997, U.S. Appln. No. 60/056,270 filed on 29-Aug-1997, U.S.  
 Appln. No. 60/056,271 filed on 29-Aug-1997, U.S. Appln. No. 60/056,247 filed on 29-Aug-1997,  
 15 U.S. Appln. No. 60/056,073 filed on 29-Aug-1997, U.S. Appln. No. 60/057,669 filed on 05-Sep-  
 1997, U.S. Appln. No. 60/057,663 filed on 05-Sep-1997, U.S. Appln. No. 60/057,626 filed on 05-  
 Sep-1997, U.S. Appln. No. 60/058,666 filed on 12-Sep-1997, U.S. Appln. No. 60/058,973 filed on  
 12-Sep-1997, U.S. Appln. No. 60/058,974 filed on 12-Sep-1997, U.S. Appln. No. 60/058,667 filed  
 on 12-Sep-1997, U.S. Appln. No. 60/060,837 filed on 02-Oct-1997, U.S. Appln. No. 60/060,862  
 20 filed on 02-Oct-1997, U.S. Appln. No. 60/060,839 filed on 02-Oct-1997, U.S. Appln. No.  
 60/060,866 filed on 02-Oct-1997, U.S. Appln. No. 60/060,843 filed on 02-Oct-1997, U.S. Appln.  
 No. 60/060,836 filed on 02-Oct-1997, U.S. Appln. No. 60/060,838 filed on 02-Oct-1997, U.S.  
 Appln. No. 60/060,874 filed on 02-Oct-1997, U.S. Appln. No. 60/060,833 filed on 02-Oct-1997,  
 U.S. Appln. No. 60/060,884 filed on 02-Oct-1997, U.S. Appln. No. 60/060,880 filed on 02-Oct-  
 25 1997, U.S. Appln. No. 60/061,463 filed on 09-Oct-1997, U.S. Appln. No. 60/061,529 filed on 09-  
 Oct-1997, U.S. Appln. No. 60/071,498 filed on 09-Oct-1997, U.S. Appln. No. 60/061,527 filed on  
 09-Oct-1997, U.S. Appln. No. 60/061,536 filed on 09-Oct-1997, U.S. Appln. No. 60/061,532 filed  
 on 09-Oct-1997, U.S. Appln. No. 60/063,099 filed on 24-Oct-1997, U.S. Appln. No. 60/063,088  
 filed on 24-Oct-1997, U.S. Appln. No. 60/063,100 filed on 24-Oct-1997, U.S. Appln. No.  
 30 60/063,387 filed on 24-Oct-1997, U.S. Appln. No. 60/063,148 filed on 24-Oct-1997, U.S. Appln.  
 No. 60/063,386 filed on 24-Oct-1997, U.S. Appln. No. 60/062,784 filed on 24-Oct-1997, U.S.  
 Appln. No. 60/063,091 filed on 24-Oct-1997, U.S. Appln. No. 60/063,090 filed on 24-Oct-1997,  
 U.S. Appln. No. 60/063,089 filed on 24-Oct-1997, U.S. Appln. No. 60/063,092 filed on 24-Oct-  
 1997, U.S. Appln. No. 60/063,111 filed on 24-Oct-1997, U.S. Appln. No. 60/063,101 filed on 24-  
 35 Oct-1997, U.S. Appln. No. 60/063,109 filed on 24-Oct-1997, U.S. Appln. No. 60/063,110 filed on

24-Oct-1997, U.S. Appln. No. 60/063,098 filed on 24-Oct-1997, U.S. Appln. No. 60/063,097 filed on 24-Oct-1997, U.S. Appln. No. 60/064,911 filed on 07-Nov-1997, U.S. Appln. No. 60/064,912 filed on 07-Nov-1997, U.S. Appln. No. 60/064,983 filed on 07-Nov-1997, U.S. Appln. No. 60/064,900 filed on 07-Nov-1997, U.S. Appln. No. 60/064,988 filed on 07-Nov-1997, U.S. Appln. No. 60/064,987 filed on 07-Nov-1997, U.S. Appln. No. 60/064,908 filed on 07-Nov-1997, U.S. Appln. No. 60/064,984 filed on 07-Nov-1997, U.S. Appln. No. 60/064,985 filed on 07-Nov-1997, U.S. Appln. No. 60/066,094 filed on 17-Nov-1997, U.S. Appln. No. 60/066,100 filed on 17-Nov-1997, U.S. Appln. No. 60/066,089 filed on 17-Nov-1997, U.S. Appln. No. 60/066,095 filed on 17-Nov-1997, U.S. Appln. No. 60/066,090 filed on 17-Nov-1997, U.S. Appln. No. 60/068,006 filed on 18-Dec-1997, U.S. Appln. No. 60/068,057 filed on 18-Dec-1997, U.S. Appln. No. 60/068,007 filed on 18-Dec-1997, U.S. Appln. No. 60/068,008 filed on 18-Dec-1997, U.S. Appln. No. 60/068,054 filed on 18-Dec-1997, U.S. Appln. No. 60/068,064 filed on 18-Dec-1997, U.S. Appln. No. 60/068,053 filed on 18-Dec-1997, U.S. Appln. No. 60/070,923 filed on 18-Dec-1997, U.S. Appln. No. 60/068,365 filed on 19-Dec-1997, U.S. Appln. No. 60/068,169 filed on 19-Dec-1997, U.S. Appln. No. 60/068,367 filed on 19-Dec-1997, U.S. Appln. No. 60/068,369 filed on 19-Dec-1997, U.S. Appln. No. 60/068,368 filed on 19-Dec-1997, U.S. Appln. No. 60/070,657 filed on 07-Jan-1998, U.S. Appln. No. 60/070,692 filed on 07-Jan-1998, U.S. Appln. No. 60/070,704 filed on 07-Jan-1998, U.S. Appln. No. 60/070,658 filed on 07-Jan-1998, U.S. Appln. No. 60/073,160 filed on 30-Jan-1998, U.S. Appln. No. 60/073,159 filed on 30-Jan-1998, U.S. Appln. No. 60/073,165 filed on 30-Jan-1998, U.S. Appln. No. 60/073,164 filed on 30-Jan-1998, U.S. Appln. No. 60/073,167 filed on 30-Jan-1998, U.S. Appln. No. 60/073,162 filed on 30-Jan-1998, U.S. Appln. No. 60/073,161 filed on 30-Jan-1998, U.S. Appln. No. 60/073,170 filed on 30-Jan-1998, U.S. Appln. No. 60/074,141 filed on 09-Feb-1998, U.S. Appln. No. 60/074,341 filed on 09-Feb-1998, U.S. Appln. No. 60/074,037 filed on 09-Feb-1998, U.S. Appln. No. 60/074,157 filed on 09-Feb-1998, U.S. Appln. No. 60/074,118 filed on 09-Feb-1998, U.S. Appln. No. 60/076,051 filed on 26-Feb-1998, U.S. Appln. No. 60/076,053 filed on 26-Feb-1998, U.S. Appln. No. 60/076,054 filed on 26-Feb-1998, U.S. Appln. No. 60/076,052 filed on 26-Feb-1998, U.S. Appln. No. 60/076,057 filed on 26-Feb-1998, U.S. Appln. No. 60/077,714 filed on 12-Mar-1998, U.S. Appln. No. 60/077,687 filed on 12-Mar-1998, U.S. Appln. No. 60/077,686 filed on 12-Mar-1998, U.S. Appln. No. 60/077,696 filed on 12-Mar-1998, U.S. Appln. No. 60/078,566 filed on 19-Mar-1998, U.S. Appln. No. 60/078,574 filed on 19-Mar-1998, U.S. Appln. No. 60/078,576 filed on 19-Mar-1998, U.S. Appln. No. 60/078,579 filed on 19-Mar-1998, U.S. Appln. No. 60/078,563 filed on 19-Mar-1998, U.S. Appln. No. 60/078,573 filed on 19-Mar-1998, U.S. Appln. No. 60/078,578 filed on 19-Mar-1998, U.S. Appln. No. 60/078,581 filed on 19-Mar-1998, U.S. Appln. No. 60/078,577 filed on 19-Mar-1998, U.S. Appln. No. 60/080,314 filed on 01-Apr-1998, U.S. Appln. No. 60/080,312 filed on

01-Apr-1998, U.S. Appln. No. 60/080,313 filed on 01-Apr-1998, U.S. Appln. No. 60/085,180 filed  
 on 12-May-1998, U.S. Appln. No. 60/085,105 filed on 12-May-1998, U.S. Appln. No. 60/085,094  
 filed on 12-May-1998, U.S. Appln. No. 60/085,093 filed on 12-May-1998, U.S. Appln. No.  
 60/085,924 filed on 18-May-1998, U.S. Appln. No. 60/085,906 filed on 18-May-1998, U.S.  
 5 Appln. No. 60/085,927 filed on 18-May-1998, U.S. Appln. No. 60/085,920 filed on 18-May-1998,  
 U.S. Appln. No. 60/085,928 filed on 18-May-1998, U.S. Appln. No. 60/085,925 filed on 18-May-  
 1998, U.S. Appln. No. 60/085,921 filed on 18-May-1998, U.S. Appln. No. 60/085,923 filed on 18-  
 May-1998, U.S. Appln. No. 60/085,922 filed on 18-May-1998, U.S. Appln. No. 60/090,112 filed  
 on 22-Jun-1998, U.S. Appln. No. 60/089,508 filed on 16-Jun-1998, U.S. Appln. No. 60/089,507  
 10 filed on 16-Jun-1998, U.S. Appln. No. 60/089,510 filed on 16-Jun-1998, U.S. Appln. No.  
 60/089,509 filed on 16-Jun-1998, U.S. Appln. No. 60/090,113 filed on 22-Jun-1998, U.S. Appln.  
 No. 60/092,956 filed on 15-Jul-1998, U.S. Appln. No. 60/092,921 filed on 15-Jul-1998, U.S.  
 Appln. No. 60/092,922 filed on 15-Jul-1998, U.S. Appln. No. 60/094,657 filed on 30-Jul-1998,  
 U.S. Appln. No. 60/095,486 filed on 05-Aug-1998, U.S. Appln. No. 60/096,319 filed on 12-Aug-  
 15 1998, U.S. Appln. No. 60/095,455 filed on 06-Aug-1998, U.S. Appln. No. 60/095,454 filed on 06-  
 Aug-1998, U.S. Appln. No. 60/097,917 filed on 25-Aug-1998, U.S. Appln. No. 60/098,634 filed  
 on 31-Aug-1998, U.S. Appln. No. 60/101,546 filed on 23-Sep-1998, U.S. Appln. No. 60/102,895  
 filed on 02-Oct-1998, U.S. Appln. No. 60/108,207 filed on 12-Nov-1998, U.S. Appln. No.  
 60/113,006 filed on 18-Dec-1998, U.S. Appln. No. 60/112,809 filed on 17-Dec-1998, U.S. Appln.  
 20 No. 60/116,330 filed on 19-Jan-1999, U.S. Appln. No. 60/119,468 filed on 10-Feb-1999, U.S.  
 Appln. No. 60/125,055 filed on 18-Mar-1999, U.S. Appln. No. 60/128,693 filed on 09-Apr-1999,  
 U.S. Appln. No. 60/130,991 filed on 26-Apr-1999, U.S. Appln. No. 60/137,725 filed on 07-Jun-  
 1999, U.S. Appln. No. 60/145,220 filed on 23-Jul-1999, U.S. Appln. No. 60/149,182 filed on 17-  
 Aug-1999, U.S. Appln. No. 60/152,317 filed on 03-Sep-1999, U.S. Appln. No. 60/152,315 filed on  
 25 03-Sep-1999, U.S. Appln. No. 60/155,709 filed on 24-Sep-1999, U.S. Appln. No. 60/163,085 filed  
 on 02-Nov-1999, U.S. Appln. No. 60/172,411 filed on 17-Dec-1999, U.S. Appln. No. 60/162,239  
 filed on 29-Oct-1999, U.S. Appln. No. 60/215,139 filed on 30-Jun-2000, U.S. Appln. No.  
 60/162,211 filed on 29-Oct-1999, U.S. Appln. No. 60/215,138 filed on 30-Jun-2000, U.S. Appln.  
 No. 60/162,240 filed on 29-Oct-1999, U.S. Appln. No. 60/215,131 filed on 30-Jun-2000, U.S.  
 30 Appln. No. 60/162,237 filed on 29-Oct-1999, U.S. Appln. No. 60/219,666 filed on 21-Jul-2000,  
 U.S. Appln. No. 60/162,238 filed on 29-Oct-1999, U.S. Appln. No. 60/215,134 filed on 30-Jun-  
 2000, U.S. Appln. No. 60/163,580 filed on 05-Nov-1999, U.S. Appln. No. 60/215,130 filed on 30-  
 Jun-2000, U.S. Appln. No. 60/163,577 filed on 05-Nov-1999, U.S. Appln. No. 60/215,137 filed on  
 30-Jun-2000, U.S. Appln. No. 60/163,581 filed on 05-Nov-1999, U.S. Appln. No. 60/215,133 filed  
 35 on 30-Jun-2000, U.S. Appln. No. 60/163,576 filed on 05-Nov-1999, U.S. Appln. No. 60/221,366

filed on 27-Jul-2000, U.S. Appln. No. 60/164,344 filed on 09-Nov-1999, U.S. Appln. No. 60/195,296 filed on 07-Apr-2000, U.S. Appln. No. 60/221,367 filed on 27-Jul-2000, U.S. Appln. No. 60/164,835 filed on 12-Nov-1999, U.S. Appln. No. 60/221,142 filed on 27-Jul-2000, U.S. Appln. No. 60/164,744 filed on 12-Nov-1999, U.S. Appln. No. 60/215,140 filed on 30-Jun-2000,  
 5 U.S. Appln. No. 60/164,735 filed on 12-Nov-1999, U.S. Appln. No. 60/221,193 filed on 27-Jul-2000, U.S. Appln. No. 60/164,825 filed on 12-Nov-1999, U.S. Appln. No. 60/222,904 filed on 03-Aug-2000, U.S. Appln. No. 60/164,834 filed on 12-Nov-1999, U.S. Appln. No. 60/224,007 filed on 04-Aug-2000, U.S. Appln. No. 60/164,750 filed on 12-Nov-1999, U.S. Appln. No. 60/215,128 filed on 30-Jun-2000, U.S. Appln. No. 60/166,415 filed on 19-Nov-1999, U.S. Appln. No.  
 10 60/215,136 filed on 30-Jun-2000, U.S. Appln. No. 60/166,414 filed on 19-Nov-1999, U.S. Appln. No. 60/219,665 filed on 21-Jul-2000, U.S. Appln. No. 60/164,731 filed on 12-Nov-1999, U.S. Appln. No. 60/215,132 filed on 30-Jun-2000, U.S. Appln. No. 60/226,280 filed on 18-Aug-2000, U.S. Appln. No. 60/256,968 filed on 21-Dec-2000, U.S. Appln. No. 60/226,380 filed on 18-Aug-2000, U.S. Appln. No. 60/259,803 filed on 05-Jan-2001, U.S. Appln. No. 60/228,084 filed on 28-Aug-2000, U.S. Appln. No. 09/915,582 filed on 27-Jul-2001, U.S. Appln. No. 60/231,968 filed on  
 15 12-Sep-2000, U.S. Appln. No. 60/236,326 filed on 29-Sep-2000, U.S. Appln. No. 60/234,211 filed on 20-Sep-2000, U.S. Appln. No. 60/226,282 filed on 18-Aug-2000, U.S. Appln. No. 60/232,104 filed on 12-Sep-2000, U.S. Appln. No. 60/234,210 filed on 20-Sep-2000, U.S. Appln. No. 60/226,278 filed on 18-Aug-2000, U.S. Appln. No. 60/259,805 filed on 05-Jan-2001, U.S. Appln.  
 20 No. 60/226,279 filed on 18-Aug-2000, U.S. Appln. No. 60/259,678 filed on 05-Jan-2001, U.S. Appln. No. 60/226,281 filed on 18-Aug-2000, U.S. Appln. No. 60/231,969 filed on 12-Sep-2000, U.S. Appln. No. 60/228,086 filed on 28-Aug-2000, U.S. Appln. No. 60/259,516 filed on 04-Jan-2001, U.S. Appln. No. 60/228,083 filed on 28-Aug-2000, U.S. Appln. No. 60/259,804 filed on 05-Jan-2001, U.S. Appln. No. 60/270,658 filed on 23-Feb-2001, U.S. Appln. No. 60/304,444 filed on  
 25 12-Jul-2001, U.S. Appln. No. 60/270,625 filed on 23-Feb-2001, U.S. Appln. No. 60/304,417 filed on 12-Jul-2001, U.S. Appln. No. 60/295,869 filed on 06-Jun-2001, U.S. Appln. No. 60/304,121 filed on 11-Jul-2001, U.S. Appln. No. 60/311,085 filed on 10-Aug-2001, U.S. Appln. No. 60/325,209 filed on 28-Sep-2001, U.S. Appln. No. 60/330,629 filed on 26-Oct-2001, U.S. Appln. No. 60/331,046 filed on 07-Nov-2001, U.S. Appln. No. 60/358,554 filed on 22-Feb-2002, U.S.  
 30 Appln. No. 60/358,714 filed on 25-Feb-2002, U.S. Appln. No. 60/277,340 filed on 21-Mar-2001, U.S. Appln. No. 60/306,171 filed on 19-Jul-2001, U.S. Appln. No. 60/278,650 filed on 27-Mar-2001, U.S. Appln. No. 60/331,287 filed on 13-Nov-2001, U.S. Appln. No. 09/950,082 filed on 12-Sep-2001, U.S. Appln. No. 09/950,083 filed on 12-Sep-2001, PCT Appln. No. US00/29363 filed on 25-Oct-2000, PCT Appln. No. US00/29360 filed on 25-Oct-2000, PCT Appln. No.  
 35 US00/29362 filed on 25-Oct-2000, PCT Appln. No. US00/29365 filed on 25-Oct-2000, PCT

Appln. No. US00/29364 filed on 25-Oct-2000, PCT Appln. No. US00/30040 filed on 01-Nov-2000, PCT Appln. No. US00/30037 filed on 01-Nov-2000, PCT Appln. No. US00/30045 filed on 01-Nov-2000, PCT Appln. No. US00/30036 filed on 01-Nov-2000, PCT Appln. No. US00/30039 filed on 01-Nov-2000, PCT Appln. No. US00/30654 filed on 08-Nov-2000, PCT Appln. No. US00/30628 filed on 08-Nov-2000, PCT Appln. No. US00/30653 filed on 08-Nov-2000, PCT Appln. No. US00/30629 filed on 08-Nov-2000, PCT Appln. No. US00/30679 filed on 08-Nov-2000, PCT Appln. No. US00/30674 filed on 08-Nov-2000, PCT Appln. No. US00/31162 filed on 15-Nov-2000, PCT Appln. No. US00/31282 filed on 15-Nov-2000, PCT Appln. No. US00/30657 filed on 08-Nov-2000, PCT Appln. No. US01/01396 filed on 17-Jan-2001, PCT Appln. No. US01/01387 filed on 17-Jan-2001, PCT Appln. No. US01/01567 filed on 17-Jan-2001, PCT Appln. No. US01/01431 filed on 17-Jan-2001, PCT Appln. No. US01/01432 filed on 17-Jan-2001, PCT Appln. No. US01/00544 filed on 09-Jan-2001, PCT Appln. No. US01/01435 filed on 17-Jan-2001, PCT Appln. No. US01/01386 filed on 17-Jan-2001, PCT Appln. No. US01/01565 filed on 17-Jan-2001, PCT Appln. No. US01/01394 filed on 17-Jan-2001, PCT Appln. No. US01/01434 filed on 17-Jan-2001, PCT Appln. No. US01/01397 filed on 17-Jan-2001, PCT Appln. No. US01/01385 filed on 17-Jan-2001, PCT Appln. No. US01/01384 filed on 17-Jan-2001, PCT Appln. No. US01/01383 filed on 17-Jan-2001, PCT Appln. No. US02/05064 filed on 21-Feb-2002, PCT Appln. No. US02/05301 filed on 21-Feb-2002, U.S. Appln. No. 09/148,545 filed on 04-Sep-1998, U.S. Appln. No. 09/621,011 filed on 20-Jul-2000, U.S. Appln. No. 09/981,876 filed on 19-Oct-2001, U.S. Appln. No. 09/149,476 filed on 08-Sep-1998, U.S. Appln. No. 09/809,391 filed on 16-Mar-2001, U.S. Appln. No. 09/882,171 filed on 18-Jun-2001, U.S. Appln. No. 60/190,068 filed on 17-Mar-2000, U.S. Appln. No. 09/152,060 filed on 11-Sep-1998, U.S. Appln. No. 09/852,797 filed on 11-May-2001, U.S. Appln. No. 09/853,161 filed on 11-May-2001, U.S. Appln. No. 09/852,659 filed on 11-May-2001, U.S. Appln. No. 10/058,993 filed on 30-Jan-2002, U.S. Appln. No. 60/265,583 filed on 02-Feb-2001, U.S. Appln. No. 09/154,707 filed on 17-Sep-1998, U.S. Appln. No. 09/966,262 filed on 01-Oct-2001, U.S. Appln. No. 09/983,966 filed on 26-Oct-2001, U.S. Appln. No. 10/059,395 filed on 31-Jan-2002, U.S. Appln. No. 09/984,245 filed on 29-Oct-2001, U.S. Appln. No. 09/166,780 filed on 06-Oct-1998, U.S. Appln. No. 09/577,145 filed on 24-May-2000, U.S. Appln. No. 09/814,122 filed on 22-Mar-2001, U.S. Appln. No. 09/189,144 filed on 10-Nov-1998, U.S. Appln. No. 09/690,454 filed on 18-Oct-2000, U.S. Appln. No. 10/062,831 filed on 05-Feb-2002, U.S. Appln. No. 10/062,599 filed on 05-Feb-2002, U.S. Appln. No. 09/205,258 filed on 04-Dec-1998, U.S. Appln. No. 09/933,767 filed on 22-Aug-2001, U.S. Appln. No. 60/184,836 filed on 24-Feb-2000, U.S. Appln. No. 60/193,170 filed on 29-Mar-2000, U.S. Appln. No. 10/023,282 filed on 20-Dec-2001, U.S. Appln. No. 10/004,860 filed on 07-Dec-2001, U.S. Appln. No. 09/209,462 filed on 11-Dec-1998, U.S. Appln. No. 09/213,365 filed on 17-Dec-

1998, U.S. Appln. No. 09/627,081 filed on 27-Jul-2000, U.S. Appln. No. 09/227,357 filed on 08-Jan-1999, U.S. Appln. No. 09/983,802 filed on 25-Oct-2001, U.S. Appln. No. 09/973,278 filed on 10-Oct-2001, U.S. Appln. No. 60/239,899 filed on 13-Oct-2000, U.S. Appln. No. 09/984,490 filed on 30-Oct-2001, U.S. Appln. No. 09/776,724 filed on 06-Feb-2001, U.S. Appln. No. 09/229,982  
 5 filed on 14-Jan-1999, U.S. Appln. No. 09/669,688 filed on 26-Sep-2000, U.S. Appln. No. 60/180,909 filed on 08-Feb-2000, U.S. Appln. No. 09/236,557 filed on 26-Jan-1999, U.S. Appln. No. 09/666,984 filed on 21-Sep-2000, U.S. Appln. No. 09/820,649 filed on 30-Mar-2001, U.S. Appln. No. 60/295,558 filed on 05-Jun-2001, U.S. Appln. No. 09/244,112 filed on 04-Feb-1999, U.S. Appln. No. 09/774,639 filed on 01-Feb-2001, U.S. Appln. No. 09/969,730 filed on 04-Oct-  
 10 2001, U.S. Appln. No. 60/238,291 filed on 06-Oct-2000, U.S. Appln. No. 09/251,329 filed on 17-Feb-1999, U.S. Appln. No. 09/716,128 filed on 17-Nov-2000, U.S. Appln. No. 09/257,179 filed on 25-Feb-1999, U.S. Appln. No. 09/729,835 filed on 06-Dec-2000, U.S. Appln. No. 09/262,109 filed on 04-Mar-1999, U.S. Appln. No. 09/722,329 filed on 28-Nov-2000, U.S. Appln. No. 09/722,329 filed on 17-Jan-2002, U.S. Appln. No. 60/262,066 filed on 18-Jan-2001, U.S. Appln. No.  
 15 09/281,976 filed on 31-Mar-1999, U.S. Appln. No. 09/288,143 filed on 08-Apr-1999, U.S. Appln. No. 09/984,429 filed on 30-Oct-2001, U.S. Appln. No. 60/244,591 filed on 01-Nov-2000, U.S. Appln. No. 09/296,622 filed on 23-Apr-1999, U.S. Appln. No. 09/305,736 filed on 05-May-1999, U.S. Appln. No. 09/818,683 filed on 28-Mar-2001, U.S. Appln. No. 09/974,879 filed on 12-Oct-2001, U.S. Appln. No. 60/239,893 filed on 13-Oct-2000, U.S. Appln. No. 09/334,595 filed on 17-  
 20 Jun-1999, U.S. Appln. No. 09/348,457 filed on 07-Jul-1999, U.S. Appln. No. 09/739,907 filed on 20-Dec-2000, U.S. Appln. No. 09/938,671 filed on 27-Aug-2001, U.S. Appln. No. 09/363,044 filed on 29-Jul-1999, U.S. Appln. No. 09/813,153 filed on 21-Mar-2001, U.S. Appln. No. 09/949,925 filed on 12-Sep-2001, U.S. Appln. No. 60/232,150 filed on 12-Sep-2000, U.S. Appln. No. 09/369,247 filed on 05-Aug-1999, U.S. Appln. No. 10/062,548 filed on 05-Feb-2002, U.S.  
 25 Appln. No. 09/382,572 filed on 25-Aug-1999, U.S. Appln. No. 09/716,129 filed on 17-Nov-2000, U.S. Appln. No. 09/393,022 filed on 09-Sep-1999, U.S. Appln. No. 09/798,889 filed on 06-Mar-2001, U.S. Appln. No. 09/397,945 filed on 17-Sep-1999, U.S. Appln. No. 09/437,658 filed on 10-Nov-1999, U.S. Appln. No. 09/892,877 filed on 28-Jun-2001, U.S. Appln. No. 09/948,783 filed on 10-Sep-2001, U.S. Appln. No. 60/231,846 filed on 11-Sep-2000, U.S. Appln. No. 09/461,325 filed  
 30 on 14-Dec-1999, U.S. Appln. No. 10/050,873 filed on 18-Jan-2002, U.S. Appln. No. 60/263,230 filed on 23-Jan-2001, U.S. Appln. No. 60/263,681 filed on 24-Jan-2001, U.S. Appln. No. 10/012,542 filed on 12-Dec-2001, U.S. Appln. No. 09/482,273 filed on 13-Jan-2000, U.S. Appln. No. 60/234,925 filed on 25-Sep-2000, U.S. Appln. No. 09/984,276 filed on 29-Oct-2001, U.S. Appln. No. 09/984,271 filed on 29-Oct-2001, U.S. Appln. No. 09/489,847 filed on 24-Jan-2000,  
 35 U.S. Appln. No. 60/350,898 filed on 25-Jan-2002, U.S. Appln. No. 09/511,554 filed on 23-Feb-

2000, U.S. Appln. No. 09/739,254 filed on 19-Dec-2000, U.S. Appln. No. 09/904,615 filed on 16-Jul-2001, U.S. Appln. No. 10/054,988 filed on 25-Jan-2002, U.S. Appln. No. 09/531,119 filed on 20-Mar-2000, U.S. Appln. No. 09/820,893 filed on 30-Mar-2001, U.S. Appln. No. 09/565,391 filed on 05-May-2000, U.S. Appln. No. 09/948,820 filed on 10-Sep-2001, U.S. Appln. No. 09/591,316 filed on 09-Jun-2000, U.S. Appln. No. 09/895,298 filed on 02-Jul-2001, U.S. Appln. No. 09/618,150 filed on 17-Jul-2000, U.S. Appln. No. 09/985,153 filed on 01-Nov-2001, U.S. Appln. No. 09/628,508 filed on 28-Jul-2000, U.S. Appln. No. 09/997,131 filed on 30-Nov-2001, U.S. Appln. No. 09/661,453 filed on 13-Sep-2000, U.S. Appln. No. 10/050,882 filed on 18-Jan-2002, U.S. Appln. No. 09/684,524 filed on 10-Oct-2000, U.S. Appln. No. 10/050,704 filed on 18-Jan-2002, U.S. Appln. No. 09/726,643 filed on 01-Dec-2000, U.S. Appln. No. 10/042,141 filed on 11-Jan-2002, U.S. Appln. No. 09/756,168 filed on 09-Jan-2001, U.S. Appln. No. 09/781,417 filed on 13-Feb-2001, U.S. Appln. No. 10/060,255 filed on 01-Feb-2002, U.S. Appln. No. 09/789,561 filed on 22-Feb-2001, U.S. Appln. No. 09/800,729 filed on 08-Mar-2001, U.S. Appln. No. 09/832,129 filed on 11-Apr-2001, PCT Appln. No.US98/04482 filed on 06-Mar-1998, PCT Appln. No.US98/04493 filed on 06-Mar-1998, PCT Appln. No.US98/04858 filed on 12-Mar-1998, PCT Appln. No.US98/05311 filed on 19-Mar-1998, PCT Appln. No.US98/06801 filed on 07-Apr-1998, PCT Appln. No.US98/10868 filed on 28-May-1998, PCT Appln. No.US98/11422 filed on 04-Jun-1998, PCT Appln. No.US01/05614 filed on 21-Feb-2001, PCT Appln. No.US98/12125 filed on 11-Jun-1998, PCT Appln. No.US98/13608 filed on 30-Jun-1998, PCT Appln. No.US98/13684 filed on 07-Jul-1998, PCT Appln. No.US98/14613 filed on 15-Jul-1998, PCT Appln. No.US98/15949 filed on 29-Jul-1998, PCT Appln. No.US98/16235 filed on 04-Aug-1998, PCT Appln. No.US98/17044 filed on 18-Aug-1998, PCT Appln. No.US98/17709 filed on 27-Aug-1998, PCT Appln. No.US98/18360 filed on 03-Sep-1998, PCT Appln. No. US02/01109 filed on 17-Jan-2002, PCT Appln. No.US98/20775 filed on 01-Oct-1998, PCT Appln. No.US98/21142 filed on 08-Oct-1998, PCT Appln. No.US98/22376 filed on 23-Oct-1998, PCT Appln. No.US98/23435 filed on 04-Nov-1998, PCT Appln. No.US98/27059 filed on 17-Dec-1998, PCT Appln. No.US99/00108 filed on 06-Jan-1999, PCT Appln. No.US99/01621 filed on 27-Jan-1999, PCT Appln. No.US99/02293 filed on 04-Feb-1999, PCT Appln. No.US99/03939 filed on 24-Feb-1999, PCT Appln. No.US99/05721 filed on 11-Mar-1999, PCT Appln. No.US99/05804 filed on 18-Mar-1999, PCT Appln. No.US99/09847 filed on 06-May-1999, PCT Appln. No.US99/13418 filed on 15-Jun-1999, PCT Appln. No.US99/15849 filed on 14-Jul-1999, PCT Appln. No.US01/00911 filed on 12-Jan-2001, PCT Appln. No.US01/29871 filed on 24-Sep-2001, PCT Appln. No.US99/17130 filed on 29-Jul-1999, PCT Appln. No.US99/19330 filed on 24-Aug-1999, PCT Appln. No.US99/22012 filed on 22-Sep-1999, PCT Appln. No.US99/26409 filed on 09-Nov-1999, PCT Appln. No.US99/29950 filed on 16-Dec-1999, PCT Appln. No.US00/00903 filed on



18-Jan-2000, PCT Appln. No.US00/03062 filed on 08-Feb-2000, PCT Appln. No.US00/06783  
filed on 16-Mar-2000, PCT Appln. No.US00/08979 filed on 06-Apr-2000, PCT Appln.  
No.US00/15187 filed on 02-Jun-2000, PCT Appln. No.US00/19735 filed on 20-Jul-2000, PCT  
Appln. No.US00/22325 filed on 16-Aug-2000, PCT Appln. No.US00/24008 filed on 31-Aug-  
5 2000, PCT Appln. No.US00/26013 filed on 22-Sep-2000, PCT Appln. No.US00/28664 filed on  
17-Oct-2000, US Appln. No. 09/833,245 filed on 12-Apr-2001, and PCT Appln. No. US01/11988  
filed on 12-Apr-2001, US Appln. No. 10/100,683 filed 19-Mar-2002, PCT Appln. No.  
US02/08278 filed on 19-Mar-2002, PCT Appln. No. US02/08279 filed on 19-Mar-2002, PCT  
Appln. No. US02/08123 filed on 19-Mar-2002, PCT Appln. No. US02/09785 filed on 19-Mar-  
10 2002, PCT Appln. No. US02/08276 filed on 19-Mar-2002, PCT Appln. No. US02/08277 filed on  
19-Mar-2002, and PCT Appln. No. US02/08124 filed on 19-Mar-2002.